**Janssen Research & Development**

**Clinical Study Report Synopsis**
**[Protocol 28431754DIA3005; Phase 3]**

**JNJ-28431754 (Canagliflozin)**

Redaction and Removal of Information in This Document

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

## SYNOPSIS

**Issue Date:** 01 February 2013

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

**Protocol No.:** 28431754DIA3005

**Title of Study:** A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin as Monotherapy in the Treatment of Subjects With Type 2 Diabetes Mellitus Inadequately Controlled With Diet and Exercise (52-Week Double-Blind Treatment Phase)

**Study Name:** CANTATA-M

**EudraCT Number:** 2009-015883-32

**NCT No.:** NCT01081834

**Clinical Registry No.:** CR017011

**Coordinating Investigator(s):** [redacted] MD, PhD, [redacted] Sweden

**Study Center(s):** A total of 90 sites participated, 33 of which were in North America (26 in the United States and 7 in Mexico), 29 of which were in Europe[a] (2 in Austria, 3 in Estonia, 7 in Lithuania, 1 in Iceland, 4 in Poland, 4 in Romania, 4 in Spain, and 4 in Sweden), 10 of which were in Central/South America (5 in Columbia and 5 in Guatemala) and 18 of which were in the rest of world (ROW) (4 in the Philippines, 3 in South Africa, 3 in India, 5 in South Korea, and 3 in Malaysia).

**Publication (Reference):**

Stenlöf K, Cefalu WT, Kim K-A, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab. 2013 Jan 24. doi: 10.1111/dom.12054.

Stenlof K, Cefalu WT, Tong C, Yee J, Sha S, Alba M, Canovatchel B, Meininger G. "Canagliflozin, a Sodium-Glucose Co-Transporter 2 Inhibitor, Improves Glycemic Control in Subjects With Type 2 Diabetes Inadequately Controlled With Diet and Exercise" [abstract]. Diabetologia. 2012 Oct;55(Suppl 1):S312-S313. Abstract No. 760. Poster presented at 48th Annual Meeting of the European Association for the Study of Diabetes (EASD), in Berlin, Germany on 10/3/2012 from 1:15pm - 2:15pm Number: 760 Session: PS 058 SGLT-2 III.

Stenlöf K, Cefalu WT, Alba M, Usiskin K, Zhao Y, Canovatchel W. "Canagliflozin, a Sodium Glucose Co-Transporter 2 Inhibitor, Improves Glycemic Control and Lowers Body Weight in Subjects With Type 2 Diabetes Inadequately Controlled With Diet and Exercise." Diabetes. 2012;61(suppl 1). Abstract 81-OR. Oral presentation at: American Diabetes Association 72nd Scientific Session;

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

June 8-12, 2012; Philadelphia, PA on 6/9/12 from 2:45pm-3:00pm during the 1:45pm-3:45pm Oral Session: "SGLT-Inhibitors."

Polidori D, Zhao Y, Alba M, Ferrannini E. "Treatment with Canagliflozin (CANA), a Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitor, for 26 Weeks Improves Indices of Beta-cell Function (BCF)." Diabetes. 2012;61(suppl 1). Abstract 1032-P. Poster presented at: American Diabetes Association 72nd Scientific Session, June 8-12, 2012, Philadelphia, PA on 6/9/12 from 11:30am-12:30pm Category: 01-D "Clinical Therapeutics/New Technology - Pharmacologic Treatment of Diabetes or its Complications."

Stenlof K, Cefalu WT, Tong C, Sha S, Yee J, Alba M, Canovatchel B, Meininger G. "Canagliflozin, a Sodium Glucose Co-Transporter 2 Inhibitor, Improves Glycemic Control and Lowers Body Weight in Subjects With Type 2 Diabetes Inadequately Controlled With Diet and Exercise." Encore Poster presented at: 4th Biennial World Congress on Controversies in Diabetes, Obesity and Hypertension (CODHy) November 8-11, 2012 in Barcelona, Spain.

Woo V, Davies MJ, de Zeeuw D, Bakris G, Usiskin K, Gassmann-Mayer C, Meininger G. "Efficacy and Safety of Canagliflozin in Subjects With Type 2 Diabetes With Moderate Renal Impairment." Poster presented at: 4th Biennial World Congress on Controversies in Diabetes, Obesity and Hypertension (CODHy) November 8-11, 2012 in Barcelona, Spain. Note: includes ISE/ISS pooled data from DIA3004, 3005, 3008 & 3010.

**Study Period:** 08 February 2010 to 20 March 2012; Week 52 database lock on 01 June 2012

**Phase of Development:** Phase 3

Objectives: This study was designed to assess the efficacy, safety and tolerability of canagliflozin monotherapy in subjects with type 2 diabetes mellitus (T2DM) who were inadequately controlled with diet and exercise. The study was composed of a Main Study and a High Glycemic Substudy. The primary objective of the Main Study was to assess the effect of canagliflozin relative to placebo on glycosylated hemoglobin ($HbA_{1c}$) after 26 weeks of treatment, and to assess the safety and tolerability of canagliflozin. This Clinical Study Report (CSR) covers the results for the Main Study through the Week 52 Visit. In addition to data included in the 26-week double-blind core period CSR (Week 26 CSR), this CSR includes data collected during the 26-week active controlled double-blind extension period (Week 26 to 52). Since the High Glycemic Substudy completed at Week 26, data from this substudy are described in the Week 26 CSR and are not described in this Week 52 CSR.

Additional objectives related to efficacy were to assess the effect of canagliflozin after 26 (relative to placebo) and 52 weeks of treatment on: glycemic control (ie, $HbA_{1c}$ and fasting plasma glucose [FPG]), body weight, the proportion of subjects with a $HbA_{1c}$ <7.0% and <6.5%, systolic blood pressure (SBP) and diastolic blood pressure (DBP), and fasting plasma lipids (including low-density lipoprotein-cholesterol [LDL-C], high-density lipoprotein-cholesterol [HDL-C], total cholesterol, the ratio of LDL-C to HDL-C, and triglycerides).

Additional objectives, including assessment through Week 26 only, evaluated the effect of canagliflozin relative to placebo on postprandial plasma glucose (PPG) concentrations (including 1-, and 2-hour PPG and glucose area under the curve [AUC]), fasting measures of beta-cell function (ie, measure of beta-cell function obtained using Homeostasis Model Assessment [HOMA2-%B] and the proinsulin/insulin ratio), and measures of insulin secretion (including insulinogenic index, AUC C-peptide/AUC glucose, and model based assessment of beta-cell function) and insulin sensitivity (in a subset of subjects [~50%] at selected sites who underwent a frequently-sampled mixed-meal tolerance test [FS-MMTT], using a minimal-model-based approach that accounts for urinary glucose excretion [UGE]). A detailed discussion of these assessments conducted through Week 26 only is restricted to the Week 26 CSR.

Safety and tolerability were assessed through Week 52.

**Methodology:** This study was a Phase 3 randomized, double-blind, placebo-controlled, 3-arm parallel-group, global multicenter study that evaluated the efficacy, safety and tolerability of canagliflozin monotherapy in subjects with T2DM who were inadequately controlled with diet and exercise. This study included a 52-week Main study (comprised of a 26-week double-blind placebo-controlled core period followed by a 26-week double-blind, active-controlled extension period that enrolled subjects with a baseline $HbA_{1c}$ ≥7.0% and ≤10.0), and a 26-week High Glycemic Substudy that enrolled subjects with a $HbA_{1c}$ value >10% and ≤12% that were randomized to canagliflozin 100 mg or 300 mg, without a placebo group. The High Glycemic Substudy is not discussed further in this report, as subjects enrolled in this substudy did not enter the extension period and, therefore, substudy data are not included in this report. Hereafter in this CSR, "study" refers to the main study.

It was planned that approximately 450 subjects with T2DM who had inadequate glycemic control with diet and exercise would be randomly assigned in a 1:1:1 ratio to once-daily administration of canagliflozin 100 mg capsules, canagliflozin 300 mg capsules, or matching placebo capsules at entry into the 26-week double-blind core period. At entry into the extension period, subjects in the canagliflozin group (100 mg or 300 mg) continued treatment, while subjects on placebo were switched to active therapy in a blinded fashion (treatment with sitagliptin 100 mg over encapsulated to match double-blind canagliflozin and placebo capsules). No hypothesis testing was specified for the Week 52 endpoints.

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, 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):** It was planned to enroll approximately 450 subjects into the study (randomly assigned to placebo, canagliflozin 100 mg and canagliflozin 300 mg in a 1:1:1 ratio). A total of 587 subjects were randomized to placebo, canagliflozin 100 mg and canagliflozin 300 mg in a 1:1:1 manner. With the permuted block randomization design of the study, the total number of subjects between treatment groups remained balanced despite the higher than anticipated enrollment. Therefore the global over enrollment had minimal impact on the planned statistical analysis for this study. The numbers of subjects included in the various analysis sets by treatment group are summarized below. The High Glycemic Substudy (discussed in detail in the Week 26 CSR) did not contribute to over enrollment.

**Summary of Analysis Sets and Disposition**

(Study 28431754-DIA3005: All Randomized Subjects Analysis Set)

| ' | Pbo/Sita (N=194) n (%) | Cana 100 mg (N=196) n (%) | Cana 300 mg (N=197) n (%) | Cana Total (N=393) n (%) | Total (N=587) n (%) |
|---|---|---|---|---|---|
| Subjects who were randomized | 194 (100) | 196 (100) | 197 (100) | 393 (100) | 587 (100) |
| Subjects who were randomized, but not dosed | 2 ( 1.0) | 1 ( 0.5) | 0 | 1 ( 0.3) | 3 ( 0.5) |
| Subjects in the mITT analysis set | 192 (99.0) | 195 (99.5) | 197 (100) | 392 (99.7) | 584 (99.5) |
| Subjects in the mITT analysis set who discontinued before the Week 52 visit | 57 (29.4) | 43 (21.9) | 32 (16.2) | 75 (19.1) | 132 (22.5) |
| Subjects in the mITT analysis set who received rescue therapy before the Week 52 visit | 63 (32.5) | 27 (13.8) | 14 ( 7.1) | 41 (10.4) | 104 (17.7) |
| Subjects in the extension mITT analysis seta | 119 (61.3) | 166 (84.7) | 166 (84.3) | 332 (84.5) | 451 (76.8) |
| Subjects in the Week 52 completers' analysis set[b] | 89 (45.9) | 129 (65.8) | 153 (77.7) | 282 (71.8) | 371 (63.2) |
| Subjects in the safety analysis set | 192 (99.0) | 195 (99.5) | 197 (100) | 392 (99.7) | 584 (99.5) |
| Subjects in the extension safety analysis set[c] | 155 (79.9) | 170 (86.7) | 170 (86.3) | 340 (86.5) | 495 (84.3) |

Key: Cana=canagliflozin; mITT=modified intent-to-treat; Pbo=placebo, Sita=sitagliptin

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

[a] Includes mITT subjects who entered extension and didn't receive rescue medication in core period.
[b] Includes mITT subjects who completed the Week 52 visit and had not initiated rescue medication.
[c] Includes mITT subjects who entered extension. This analysis set is used in the Week 26 to Week 52 safety analysis.
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**Diagnosis and Main Criteria for Inclusion:** Man or woman ≥18 and ≤80 years of age with T2DM who met 1 of the 2 following criteria:

- Not on an antihyperglycemic agent (AHA) at screening (off for at least 12 weeks) with a $HbA_{1c}$ ≥7.0% and ≤10.0% at the screening (or prescreening) visit (Note: if $HbA_{1c}$ measurement was not within 3 weeks of the Week -2 visit, $HbA_{1c}$ testing was to be repeated at the Week -2 visit to assess this inclusion criterion); or
- On an oral AHA in monotherapy (except a peroxisome proliferator-activated receptor gamma (PPARγ) agonist, eg, thiazolidinedione [TZD]) or on low dose combination therapy with metformin (≤1,000 mg) and sulphonylurea (SU) (at ≤50% of maximally or near maximally effective doses with a $HbA_{1c}$ ≥6.5% and ≤9.5% at the screening (or prescreening) visit and had a Week -2 (after the 8 week diet and exercise and AHA washout period) $HbA_{1c}$ ≥7.0% and ≤10.0% and FPG <270 mg/dL (15 mmol/L).

**Test Product, Dose and Mode of Administration, Batch No.:** Canagliflozin capsules containing active 100 mg (batch/lot nos.: PD3093, PD3092, 09J30/G002, 09K06 G002, PD3389, PD3387, PD3388, 32783.1) or 300 mg (batch/lot nos.: PD3155, PD3156, PD3158, PD3401, PD3394, 30845.3, 30845.6, PD3403, 30845.14, PD3305, 32783.8) tablets for oral administration.

**Reference Therapy, Dose and Mode of Administration, Batch No.:** Placebo to match canagliflozin (batch/lot nos.: PD3221, PD3220, 30845.8, 09L16/G001, 10B22/G001, 30845.2, 32580.4) and commercially available sitagliptin supplied by the sponsor (PD3280, 30485.2, 30009.1, 10C31/G018, 32783.9).

**Duration of Treatment:** The total duration of the study, including the optional prescreening visit, the 26-week placebo-controlled, double-blind treatment period, the 26-week double-blind, active-controlled extension period, and the 4-week follow-up period, was approximately 60 weeks (for subjects not on an AHA at the screening visit) to 68 weeks (for subjects on an AHA who washed off of their AHA during the 8-week diet and exercise and AHA washout period).

A separate CSR (Week 26 CSR) summarized the results of the 26-week double-blind core period. This report summarizes the results of the 52-week double-blind treatment phase (including the 26-week double-blind treatment period and the 26-week extension double-blind treatment period), referred to as the entire double-blind treatment phase.

**Evaluations:**

The key efficacy measure at Week 52 was $HbA_{1c}$. Additional measures of efficacy at Week 52 included FPG; body weight, body mass index (BMI) and waist circumference; SBP and DBP; fasting plasma lipids (LDL-C, HDL-C, non-HDL-C, total cholesterol, and triglycerides) and use of rescue medication.

Refer to the Week 26 CSR for a description of the measurement of postprandial plasma glucose (PPG) concentrations (including 1- and 2-hour PPG and glucose AUC) following a mixed-meal tolerance test (MMTT), during which a timed urine collection was performed to measure urine glucose and urine creatinine, and obtainment of frequently-sampled measurements for glucose, C-peptide and insulin in a subset of subjects during a FS-MMTT to assess indices of insulin and indices of insulin sensitivity and other pharmacodynamic assessments (UGE and renal threshold for UGE) during the 26-week double-blind core period.

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

Refer to the Week 26 CSR for a description of plasma concentration measurements for pharmacokinetic evaluations in a subgroup of subjects and sample collection for pharmacogenomic testing for the 26-week double-blind core period.

**Statistical Methods:**

Sample Size Determination

Sample size determination was based on the primary endpoint (change in $HbA_{1c}$ from baseline) at Week 26, as discussed in the Week 26 CSR. No study hypotheses were tested for evaluation at the Week 52 timepoint.

*Efficacy:*

The primary efficacy analysis of changes from baseline in $HbA_{1c}$ at Week 26 and key secondary endpoints are described in the Week 26 CSR.

The last observation carried forward (LOCF) method was applied when the Week 52 values were missing. In subjects receiving rescue medication, their measurements made before rescue were used as the last observations.

An ANCOVA, model with treatment (canagliflozin 100 mg and canagliflozin 300 mg) and stratification factors (whether or not a subject was taking AHA[s] at screening and whether or not a subject participated in the FS-MMTT) as fixed effects, and the corresponding baseline value as a covariate based on the modified intent-to-treat (mITT) analysis set and extension mITT analysis sets was used to evaluate changes or percent changes from baseline at Week 52 in the following continuous efficacy variables: $HbA_{1c}$; FPG; body weight; SBP; DBP; fasting plasma lipids, including LDL-C, HDL-C, non-HDL-C, total cholesterol, ratio of LDL-C to HDL-C, and triglycerides; and waist circumference and BMI. The least-squares (LS) means for the change from baseline values at Week 52 and each timepoint through Week 52, and their 2-sided 95% confidence intervals (CIs) were estimated based on the ANCOVA model for the canagliflozin 300 mg and 100 mg groups. No treatment differences (and the associated CIs and p values) were calculated for the Week 52 analysis.

The categorical secondary efficacy endpoints (proportion of subjects with $HbA_{1c}$ <6.5% and <7.0% and subjects with at least 5% body weight reduction) were summarized by treatment group at Week 52. No treatment differences were calculated.

*Pharmacodynamics:* No pharmacodynamic studies were performed during the extension period. Please refer to the Week 26 CSR for detail regarding related statistical methodology and results of pharmacodynamic assessment of beta-cell function, UGE and insulin sensitivity during a FS-MMTT.

*Safety:* The incidence (ie, number and percent of subjects with 1 or more adverse event in each category) of adverse events, serious adverse events, deaths, adverse events leading to discontinuation, drug-related adverse events, serious drug-related adverse events, drug-related adverse events leading to discontinuation of study drug, serious adverse events leading to discontinuation of study drug, and serious drug-related adverse events were summarized by treatment group for the entire double-blind treatment phase (ie, Day 1 to Week 52) and for the extension double blind period (ie, Week 26 to Week 52). Specific adverse events that were predefined in the protocol as requiring the collection of additional information, to support additional analysis (eg, time to first event), included urinary tract infection (UTI) adverse events and male and female genital infections. Safety analyses for overall and specific adverse

events were performed including all data, regardless of the initiation of rescue medication. Analyses and summaries of hypoglycemic episodes were provided for both *prior to initiation of glycemic rescue medication* and *regardless of use of glycemic rescue medication*. Predefined limits of change (PDLCs) and descriptive statistics were provided for other safety parameters for the entire double-blind treatment phase, including all data, regardless of the initiation of rescue medication.

Summaries of laboratory parameters, vital signs and ECGs (including PDLCs) from baseline to Week 52 were provided.

**RESULTS:**

STUDY POPULATION:

**Subject and Treatment Information and Baseline Characteristics**

A total of 1,667 subjects were screened, and a total of 587 subjects were randomized into the Main Study. There were 584 mITT subjects (randomized subjects who received at least 1 dose of double-blind study medication), of whom 451 (77%) subjects entered the extension period and did not take rescue medications in the core period, comprising the extension mITT analysis set. The mITT analysis set and the safety analysis set (mITT, as treated) were identical. The 52-week completers' analysis set excludes subjects who were rescued prior to the Week 52 visit (n=104) or who discontinued double-blind study drug before the Week 52 visit (n=132); overall, 371 subjects were in the completer's population (note: some subjects were rescued and then did not complete the 52 double-blind week treatment phase). As shown in the tabular summary below, throughout the 52-week study period, a higher proportion of subjects in the placebo/sitagliptin group (30%) discontinued the study as compared to either the canagliflozin 100 mg (22%) or 300 mg (16%) group. The most frequent reason for discontinuation was "Other" (nearly 7%, occurring more frequently in the placebo/sitagliptin group).

**Reasons for Discontinuation**
(Study 28431754-DIA3005: Modified Intent-to-Treat Analysis Set)

| | Pbo/Sita (N=192) n (%) | Cana 100 mg (N=195) n (%) | Cana 300 mg (N=197) n (%) | Cana Total (N=392) n (%) | Total (N=584) n (%) |
|---|---|---|---|---|---|
| **Total number of subjects discontinued** | 57 (29.7) | 43 (22.1) | 32 (16.2) | 75 (19.1) | 132 (22.6) |
| **Primary reason for discontinuation**[a] | | | | | |
| Adverse event | 2 ( 1.0) | 5 ( 2.6) | 4 ( 2.0) | 9 ( 2.3) | 11 ( 1.9) |
| Creatinine or eGFR withdrawal criteria | 1 ( 0.5) | 4 ( 2.1) | 0 | 4 ( 1.0) | 5 ( 0.9) |
| Death | 2 ( 1.0) | 1 ( 0.5) | 0 | 1 ( 0.3) | 3 ( 0.5) |
| Lack of efficacy on rescue therapy | 12 ( 6.3) | 2 ( 1.0) | 0 | 2 ( 0.5) | 14 ( 2.4) |
| Lost to Follow-Up | 6 ( 3.1) | 6 ( 3.1) | 6 ( 3.0) | 12 ( 3.1) | 18 ( 3.1) |
| Noncompliance with study drug | 3 ( 1.6) | 4 ( 2.1) | 2 ( 1.0) | 6 ( 1.5) | 9 ( 1.5) |
| Physician decision | 0 | 1 ( 0.5) | 1 ( 0.5) | 2 ( 0.5) | 2 ( 0.3) |
| Pregnancy | 1 ( 0.5) | 0 | 0 | 0 | 1 ( 0.2) |
| Protocol violation | 0 | 6 ( 3.1) | 1 ( 0.5) | 7 ( 1.8) | 7 ( 1.2) |
| Withdrawal of consent | 9 ( 4.7) | 4 ( 2.1) | 8 ( 4.1) | 12 ( 3.1) | 21 ( 3.6) |
| Unable to take protocol defined rescue therapy | 2 ( 1.0) | 0 | 1 ( 0.5) | 1 ( 0.3) | 3 ( 0.5) |
| Other | 19 ( 9.9) | 10 ( 5.1) | 9 ( 4.6) | 19 ( 4.8) | 38 ( 6.5) |

[a] As indicated by the investigator on the eCRF for MITT subjects who discontinued before the Week 52 visit.
Key: Cana=canagliflozin, eCRF=estimated glomerular filtration rate, Pbo=placebo, Sita=sitagliptin
Note: Percentages were calculated with the number of subjects in each group as the denominator.
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The rate of discontinuations was lower for subjects during the extension period (extension safety analysis set) relative to the entire double-blind treatment phase (mITT analysis set): 12.9% in the placebo/sitagliptin group, 6.8% in the canagliflozin combined group, and 8.7% over all treatments. The overall mean duration of subject exposure (prior to rescue medication) for subjects in the mITT analysis set over the entire double-blind treatment phase was greater in the canagliflozin groups compared with

placebo/sitagliptin, with 72% of subjects in the canagliflozin groups having at least 50 weeks of exposure, relative to 46% of subjects in the placebo/sitagliptin group. This difference was driven by the higher proportion of subjects in the placebo/sitagliptin group being rescued during the entire double-blind treatment phase. Indeed, the overall mean duration of subject exposure, including exposure after initiation of rescue was generally similar across treatment groups, and only slightly shorter in the placebo/sitagliptin group (44 weeks) relative to canagliflozin (46% for the combined canagliflozin group), likely due to the slightly higher discontinuation rate observed in the placebo/sitagliptin group. The overall mean duration of subject exposure (regardless of rescue medication) for subjects in the extension safety set over the 26 -week double-blind extension period was similar across all treatment groups, ranging from 50 weeks in the placebo/sitagliptin and canagliflozin 100 mg groups to 52 weeks in the canagliflozin 300 mg group.

**Baseline Characteristics**

Baseline demographic characteristics for the mITT analysis set were generally similar across treatment groups. The median age of subjects in the study was 56 years (range: 24 to 79 years), and a higher proportion of women than men were randomized. Almost 70% of the subjects were white, with approximately 15% of subjects Asians, and 7% of subjects black or African-American; approximately 30% of subjects were of Hispanic or Latino ethnicity. The mean baseline $HbA_{1c}$ was 8.0%, and the median diabetes duration was 3.0 years (range: 0 to 26 years). Baseline mean weight was 86.8 kg and baseline mean BMI was 31.6 $kg/m^2$ for subjects in the mITT analysis set; these characteristics were generally similar across treatment groups, with more than half of the subjects being obese (BMI ≥30 $kg/m^2$) based upon National Institutes of Health criteria (NIH 1998). The baseline demographic and anthropometric characteristics of subjects in the extension mITT analysis set and extension safety analysis set were highly consistent with those of subjects in the mITT analysis set.

EFFICACY RESULTS:

*Primary Endpoint:*

In the extension mITT analysis set, the LS mean change from baseline in $HbA_{1c}$ at Week 52 was -1.11% for the canagliflozin 300 mg group and -0.81% for the canagliflozin 100 mg group (see table below). In both treatment groups, a rapid decrease from baseline in $HbA_{1c}$ was observed through Week 12, followed by a further but more gradual decline through Week 34, and a small increase thereafter. The results for the mITT analysis set were similar to those for the extension mITT analysis set, with only slightly smaller reductions from baseline in $HbA_{1c}$ for both canagliflozin 300 mg (-1.04%) and 100 mg (-0.75%) seen in the mITT analysis set.

*Secondary Endpoints:*

Substantial improvements (in the proportion of subjects to <7.0% $HbA_{1c}$ goal and FPG) were seen, with greater reductions seen with canagliflozin 300 mg relative to canagliflozin 100 mg. In addition to improvements in glucose control, reductions in body weight and in SBP, and increases in HDL-C were seen with canagliflozin, as well as an increase in LDL-C, but with no change in the LDL-C/HDL-C ratio.

**Change from Baseline to Week 52 for Efficacy Endpoints - LOCF**
(Study 28431754-DIA3005: Extension mITT Analysis Set)

| | ----------Cana 100 mg --------- | | ----------Cana 300 mg ---------- | |
|---|---|---|---|---|
| Endpoints | LS Mean | (95% CI) | LS Mean | (95% CI) |
| $HbA_{1c}$ Change (%) | -0.81 | (-0.938; -0.682) | -1.11 | (-1.238; -0.981) |
| Achieving 7% $HbA_{1c}$ target (%) | 52.4 | (44.8, 60.0) | 64.5 | (57.2, 71.8) |
| FPG Change (mmol/L) | -1.52 | (-1.767; -1.279) | -2.17 | (-2.416; -1.927) |
| Body Weight Percent Change (%) | -3.3 | (-3.9; -2.6) | -4.4 | (-5.1; -3.7) |
| Systolic BP Change (mmHg) | -1.42 | (-2.987; 0.155) | -3.91 | (-5.481; -2.330) |
| HDL-C Percent Change (%) | 11.1 | (8.2; 14.0) | 14.7 | (11.8; 17.5) |
| Triglycerides Percent Change (%) | -2.0 | (-8.0; 4.0) | -2.1 | (-8.1; 3.9) |
| LDL-C Percent Change (%) | 6.3 | (2.2; 10.3) | 11.2 | (7.2; 15.3) |

Key: cana=canagliflozin, CI=confidence interval, $HbA_{1c}$=glycosylated hemoglobin, FPG=fasting plasma glucose, HDL-C=high- density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, LS=least-squares

Note: For continuous endpoints, the within-in group least-squares mean change from baseline and CI are based on ANCOVA models with terms for treatment and stratification factor and adjusting for the baseline value as a covariate. For achieving 7% $HbA_{1c}$ target, CI is based on the binomial distribution.

SAFETY RESULTS:

*Adverse Events*: Over the entire double-blind treatment phase, the overall incidence of subjects with adverse events for the safety analysis set in the canagliflozin 100 mg and 300 mg groups was similar (67.2% and 66.0%, respectively) compared with the placebo/sitagliptin group (64.1%), with a higher incidence of drug-related adverse events in both canagliflozin groups compared with the placebo/sitagliptin group also observed. The overall higher rate of drug-related adverse events was largely due to a higher incidence of several specific adverse events discussed below. The overall incidence of adverse events leading to discontinuation was low and slightly higher in the canagliflozin groups than in the placebo/sitagliptin group; the rate of drug-related adverse events leading to discontinuation was low across all treatment groups and slightly higher in the canagliflozin groups relative to the placebo/sitagliptin group. The incidence of serious adverse events was similar in the canagliflozin 100 mg and placebo/sitagliptin group, with a lower incidence observed in the canagliflozin 300 mg group. There were 3 deaths (0.5% of subjects) reported (2 subjects in the placebo/sitagliptin group and 1 subject in the canagliflozin 100 mg group) during the double-blind treatment phase. The overall incidence of adverse events that occurred in the extension period (Week 26 to Week 52) was low and slightly greater in the placebo/sitagliptin group relative to the canagliflozin groups. A modestly higher incidence of drug-related adverse events was seen in the canagliflozin 100 mg, but not the 300 mg group, relative to the placebo/sitagliptin group. There were no adverse events leading to discontinuation in the canagliflozin group during the extension period; no substantive differences in other classes of adverse events were noted.

**Adverse Events During the Entire Double-Blind Treatment Phase - Regardless of Rescue Medication**
(Study 28431754-DIA3005: Safety Analysis Set)

| Number (%) of subjects with at least one adverse event of the following Types | Pbo/Sita (N=192) n (%) | Cana 100 mg (N=195) n (%) | Cana 300 mg (N=197) n (%) | Cana Total (N=392) n (%) |
|---|---|---|---|---|
| Any adverse events | 123 (64.1) | 131 (67.2) | 130 (66.0) | 261 (66.6) |
| Adverse events leading to discontinuation | 2 ( 1.0) | 6 ( 3.1) | 4 ( 2.0) | 10 ( 2.6) |
| Adverse events related to study drug* | 23 (12.0) | 44 (22.6) | 53 (26.9) | 97 (24.7) |
| Adverse events related to study drug* and leading to discontinuation | 1 ( 0.5) | 3 ( 1.5) | 4 ( 2.0) | 7 ( 1.8) |
| Serious adverse events | 11 ( 5.7) | 11 ( 5.6) | 5 ( 2.5) | 16 ( 4.1) |
| Serious adverse events leading to discontinuation | 0 | 3 ( 1.5) | 0 | 3 ( 0.8) |
| Serious adverse events related to study drug* | 1 ( 0.5) | 3 ( 1.5) | 0 | 3 ( 0.8) |
| Serious adverse events related to study drug* and leading to discontinuation | 0 | 1 ( 0.5) | 0 | 1 ( 0.3) |
| Deaths | 2 ( 1.0) | 1 ( 0.5) | 0 | 1 ( 0.3) |

[a] Related to study drug includes relationship determined by investigators: possibly related, probably related and very likely related.
Key: Cana=canagliflozin, Pbo=placebo, Sita=sitagliptin
Note: Percentages were calculated with the number of subjects in each group as the denominator.
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**Adverse Events During the Extension Period - Regardless of Rescue Medication**
(Study 28431754-DIA3005: Extension Safety Analysis Set)

| Number (%) of subjects with at least one adverse event of the following types | Pbo/Sita (N=155) n (%) | Cana 100 mg (N=170) n (%) | Cana 300 mg (N=170) n (%) | Cana Total (N=340) n (%) |
|---|---|---|---|---|
| Any adverse events | 68 (43.9) | 68 (40.0) | 62 (36.5) | 130 (38.2) |
| Adverse events leading to discontinuation | 1 ( 0.6) | 0 | 0 | 0 |
| Adverse events related to study drug[a] | 9 ( 5.8) | 15 ( 8.8) | 9 ( 5.3) | 24 ( 7.1) |
| Adverse events related to study drug[a] and leading to Discontinuation | 1 ( 0.6) | 0 | 0 | 0 |
| Serious adverse events | 7 ( 4.5) | 3 ( 1.8) | 3 ( 1.8) | 6 ( 1.8) |
| Serious adverse events leading to discontinuation | 0 | 0 | 0 | 0 |
| Serious adverse events related to study drug[a] | 1 ( 0.6) | 0 | 0 | 0 |
| Serious adverse events related to study drug[a] and leading to Discontinuation | 0 | 0 | 0 | 0 |
| Deaths | 1 ( 0.6) | 0 | 0 | 0 |

[a] Related to study drug includes relationship determined by investigators: possibly related, probably related and very likely related.
Key: Cana=canagliflozin, Pbo=placebo, Sita=sitagliptin
Note: Percentages were calculated with the number of subjects in each group as the denominator.

Over the entire double-blind treatment phase, adverse events grouped by system organ class (SOC) were reported most frequently (ie, >10% of subjects in any treatment group) for Infections and infestations, Gastrointestinal disorders, Musculoskeletal and connective tissue disorders, and Nervous system disorders SOCs. For the SOC of Reproductive system and breast disorders, an overall higher incidence of adverse events was observed in both canagliflozin groups relative to the placebo/sitagliptin group, with the 95% CI around the between-group difference from the placebo/sitagliptin group excluding "0". The overall higher incidence in this SOC was related to a higher incidence of specific adverse events of balanitis, pruritus genital, and vulvovaginal pruritus (all occurring with an incidence ≤3% in the canagliflozin groups, relative to 0% in the placebo/sitagliptin group). The adverse events that were common (incidence ≥5% in any treatment group) included the following: influenza, nasopharyngitis, upper respiratory tract infection, UTI, arthralgia, back pain, and headache. There was a dose-related increase in drug-related adverse events with canagliflozin treatment, with an incidence of 22.6% and 26/9% in the canagliflozin 100 mg and 300 mg groups, respectively, relative to an incidence in the placebo/sitagliptin group of 12.0%. These findings were mainly due to a higher incidence of drug-related

adverse events in the Infections and infestations SOC (mainly due to specific adverse events such as female genital infections) and in the Renal and urinary disorders SOC, where higher incidences of drug-related adverse events consistent with osmotic diuresis (eg, polyuria and pollakiuria) occurred in the canagliflozin 300 mg group relative to placebo/sitagliptin and canagliflozin 100 mg groups. Relative to the placebo/sitagliptin group, drug-related adverse events of the Reproductive system and breast disorders SOC were more commonly reported in the canagliflozin groups, where numerically higher incidences of several specific male and female genital infections or genital symptom-related (eg, balanitis, genital pruritus) adverse events were observed. The incidence of episodes of documented hypoglycemia was similar across treatment groups (approximately 4% to 5% in each group, with the majority of the documented episodes in the canagliflozin groups occurring in the core period, compared to the placebo/sitagliptin group, where approximately half occurred in the core period).

*Safety Laboratory Assessment:*

A few changes in laboratory safety analytes from baseline at Week 52 with canagliflozin 100 mg and 300 mg were observed, including a modest increase (approximately 5%) in hemoglobin values relative to a small decrease in the placebo/sitagliptin group (-1.0%). Modest increases in mean change from baseline in serum creatinine of approximately 4.4% to 5.2% were observed in the canagliflozin 300 mg and the placebo/sitagliptin groups, relative to a 1.8% increase observed in the canagliflozin 100 mg group. These findings were accompanied by commensurate decreases in mean eGFR. A moderate mean increase of approximately 21.0% to 22.5% in blood urea nitrogen (BUN) was observed in the canagliflozin groups, relative to a smaller increase (6.9%) in the placebo/sitagliptin group. Modest reductions in mean changes from baseline in indices of liver function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT]) were observed in both canagliflozin groups compared to the placebo/sitagliptin group through Week 52. These changes occurred concomitantly with moderate increases in mean changes from baseline in bilirubin (10.3% to 11.2%) in the canagliflozin groups relative to no discernable mean changes in the placebo/sitagliptin group. No subject in the canagliflozin group had elevations in their last ALT level >3 times the upper limit of normal, compared to 1 subject in the placebo/sitagliptin group. A moderate mean decrease in serum urate of approximately 12.5% to 14.3% was seen in both canagliflozin treatment groups at Week 52, relative to a small increase in the placebo/sitagliptin group (6.9%). A small mean increase in serum magnesium of approximately 6.0% to 7.1% was observed in the canagliflozin groups, relative to no notable change in the placebo/sitagliptin group.

*Other Safety Assessments:* Treatment with canagliflozin 100 mg and 300 mg led to modest reductions in blood pressure (systolic reduction greater than diastolic), with no meaningful change in pulse rate and ECG.

PHARMACOKINETIC, PHARMACODYNAMIC AND PHARMACOGENOMIC RESULTS

Pharmacokinetics, biomarkers, and pharmacogenomic studies were assessed at baseline and at the completion of the core study period (Week 26) and results have been previously presented in Section 7 of the Week 26 CSR. No additional pharmacokinetic, biomarker, or pharmacogenomic studies were performed during the extension period.

STUDY LIMITATIONS

A total of 678 subjects were randomized in the study, which included 587 subjects in the Main Study and 91 subjects in the High Glycemic Substudy. With the protocol defined sample size to be approximately 550, the study over enrolled 23% of the target worldwide. With the permuted block randomization design of this study, the total number of subjects between treatment groups was expected to be very well balanced. Therefore, the global over enrollment is considered to have had a minimal impact on the planned statistical analysis for this study.

CONCLUSIONS

- Over a 52-week double-blind treatment phase, canagliflozin provided clinically important and sustained glycemic improvements (in $HbA_{1c}$ change from baseline, proportion to <7.0% $HbA_{1c}$ goal, and FPG), with greater reductions seen with canagliflozin 300 mg relative to canagliflozin 100 mg. In addition to improvements in glucose control, reductions in body weight and in SBP were seen with canagliflozin, as well as an increase in LDL-C, and a small increase in HDL-C, but with no change in the LDL-C/HDL-C ratio.
- Canagliflozin was overall generally well tolerated, with a safety profile showing an increase in adverse events of genital mycotic infections, and in adverse events related to osmotic diuresis or reduced intravascular volume (eg, polyuria, pollakiuria, or postural dizziness), and a small increase in adverse events of UTI, relative to the placebo/sitagliptin group.
- Overall, this 52-week study met the key primary and secondary hypotheses, suggesting a favorable and sustained glycemic efficacy profile with both doses (with the canagliflozin 300 mg dose providing additional benefit compared with the 100 mg dose), and a safety and tolerability profile consistent with expectations.