SYNOPSIS

Issue Date: 7 September 2012

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

Protocol No.: 28431754DIA2003

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Monotherapy

EudraCT Number: 2010-024256-28

NCT No.: NCT01340664

Clinical Registry No.: CR017914

Coordinating Investigator: Ben Lasko, MD, [Contact]

Study Center(s): A total of 60 study centers participated in 7 countries, including 34 centers in North America (23 in the US, 7 in Canada, 4 in Mexico), 16 centers in Europe[a] (5 in Czech Republic, 5 in Romania, 6 in Slovakia), and 10 in the rest of the world (ROW) (10 in Russia).

Publication (Reference): None

Study Period: 27 June 2011 to 20 April 2012

Phase of Development: Phase 2

Objectives: The primary objectives were to assess the effect of canagliflozin 150 mg administered twice daily (bid) on glycosylated hemoglobin (HbA_{1c}) relative to placebo and to assess the safety and tolerability of canagliflozin after 18 weeks of treatment. The secondary objectives were to assess after 18 weeks of treatment the effect of canagliflozin 50 mg bid on HbA_{1c} relative to placebo and to assess the effect of canagliflozin 150 mg bid or canagliflozin 50 mg bid, on the following parameters relative to placebo: fasting plasma glucose (FPG), body weight, proportion of subjects with HbA_{1c} <7.0% and <6.5%, 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), systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Methodology: This Phase 2 randomized, double-blind, placebo-controlled, parallel-group, 3-arm, global multicenter study evaluated the efficacy, safety, and tolerability of canagliflozin in subjects with type 2 diabetes mellitus (T2DM) who were inadequately controlled on metformin monotherapy.

It was planned that approximately 270 adult subjects (≥18 and ≤80 years of age) with T2DM who had inadequate glycemic control (ie, HbA_{1c} of ≥7.0% to ≤10.5%) on metformin monotherapy (on a metformin dose of ≥2,000 mg/day, or ≥1,500 mg/day, if unable to tolerate a higher dose) were to be randomly assigned in a 1:1:1 ratio to the addition of treatment with canagliflozin 50 mg bid, canagliflozin 150 mg

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

bid, or matching placebo added to ongoing stable doses of metformin monotherapy and entered into the 18-week, placebo-controlled, double-blind treatment phase.

Several safety 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 and also cardiovascular (CV) events (major cardiovascular events plus events of hospitalized unstable angina [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, an Independent Data Monitoring Committee (IDMC) reviewed unblinded serious adverse event and CV 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 270 adult subjects into the study, and 279 subjects were randomly assigned to study treatment.

Diagnosis and Main Criteria for Inclusion: Man or woman ≥18 and ≤80 years of age with T2DM and on metformin monotherapy at a stable protocol-specified dose (≥2,000 mg/day [or ≥1,500 mg/day, if unable to tolerate a higher dose]) for at least 8 weeks immediately prior to screening and had an HbA_{1c} of ≥7.0% and ≤10.5% at screening (or at Week -2, if screening measurement is more than 3 weeks before Week -2).

Test Product, Dose and Mode of Administration, Batch No.: Canagliflozin capsules containing active 50 mg (batch/lot no. 11E02/G006) or 150 mg (batch/lot no. 11E09/G007) tablets for oral administration.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo to match canagliflozin (batch/lot no. 32580.4)

Duration of Treatment: The total duration of the study, including the optional prescreening visit, the 18-week double-blind treatment phase, and the 30-day follow-up posttreatment phase was approximately 26 weeks.

Evaluations:

Efficacy assessments included $HbA_{1c,}$ FPG, body weight, fasting lipid profile, SBP, and DBP.

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

Statistical Methods:

Sample Size Determination

The primary objective of this study was to demonstrate the superiority of canagliflozin (150 mg bid) to placebo as measured by the change in HbA_{1c} from baseline to Week 18. Based on the results of the Phase 2b, 12-week study in a similar population of subjects with T2DM, a group difference of 0.5% and a common standard deviation of 1.0% was assumed with respect to the change in HbA_{1c}. Using a 2-sample, 2-sided t-test with Type I error rate of 0.05, it was estimated that 85 subjects per group would be required to achieve 90% power. To account for subjects missing endpoint HbA_{1c} values (expected to be <5%), a modestly larger sample size of 90 subjects per treatment group (270 total subjects) were to be randomly assigned into this study.

Efficacy

The primary efficacy endpoint was the change in HbA_{1c} from baseline at Week 18. The last-observation-carried-forward (LOCF) method was applied when the Week 18 values were missing. An analysis of covariance (ANCOVA) model was used with treatment and the stratification factor related to glycemic control prior to randomization (ie, whether or not the Week -2 HbA_{1c} value for the subject was ≥8.0%) as fixed effects and the baseline HbA_{1c} value as a covariate. The treatment difference (canagliflozin minus placebo) in the least-squares means and their 2-sided 95% confidence interval (CI) was estimated based on this model. The p values for testing superiority in terms of HbA_{1c} were calculated by comparing the least squares (LS) means. The analyses of major secondary efficacy endpoints were performed using the mITT analysis set; analyses based on the per protocol (PP) analysis set were performed as supportive analyses.

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 leading to discontinuation were summarized by treatment group. 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. Predefined limits of change and descriptive statistics were provided for other safety parameters.

RESULTS:

STUDY POPULATION:

A total of 279 subjects were randomly assigned to study treatment. Overall, 90% of the randomly assigned subjects completed 18 weeks of treatment, with a slightly higher proportion in the placebo and canagliflozin 50 mg bid groups completing relative to the canagliflozin 150 mg bid group. The most common reason for withdrawal from the study was in the category of "Adverse Event" leading to 2.9% (8 subjects) discontinuing. The incidence of adverse events leading to discontinuation was higher in the canagliflozin 150 mg bid group (7.5% [7 subjects]) relative to the canagliflozin 50 mg bid group (1.1% [1 subject]) and the placebo group (0%). The second and third most common reasons for withdrawal from the study were in the categories of "Withdrawal of Consent" (2.2% [6 subjects]) and "Other" (1.8% [5 subjects]). The “Other” category included reasons related to relocation, extended travel, and poor compliance with study visits.

Summary of Analysis Sets and Disposition

(Study 28431754DIA2003: All Randomized Subjects Analysis Set)

	Placebo (N=93) n (%)	CANA 50 mg bid (N=93) n (%)	CANA 150 mg bid (N=93) n (%)	CANA Total (N=186) n (%)	Total (N=279) n (%)
Subjects who are randomized	93 (100)	93 (100)	93 (100)	186 (100)	279 (100)
Subjects in the mITT analysis set	93 (100)	93 (100)	93 (100)	186 (100)	279 (100)
Subjects in the safety analysis set	93 (100)	93 (100)	93 (100)	186 (100)	279 (100)
mITT subjects who discontinued before the Week 18 visit	7 (7.5)	8 (8.6)	13 (14.0)	21 (11.3)	28 (10.0)
Subjects in the Completers' analysis set	86 (92.5)	85 (91.4)	80 (86.0)	165 (88.7)	251 (90.0)
mITT subjects in the PP analysis set	86 (92.5)	84 (90.3)	79 (84.9)	163 (87.6)	249 (89.2)

Key: bid=twice daily, N=total number of subjects/sample size, n=total numbers of subjects in subgroup/size of subsample, mITT=modified intent-to-treat, PP=per protocol

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

The overall mean duration of subject exposure for the 18-week double-blind treatment phase was similar in the combined canagliflozin groups relative to placebo. Exposure was slightly less in the canagliflozin 150 mg bid group, and similar in the canagliflozin 50 mg bid and placebo groups.

Baseline Characteristics

Baseline demographic characteristics were generally similar across treatment groups. The median age of subjects was approximately 57 years, and a slightly higher proportion of women were enrolled. Consistent with the regions of the world in which subjects were recruited, 82.8% of the subjects were white, with approximately 6.5% of subjects Asian, and 3.6% of subjects black or African American (9.6% of subjects randomized in the US were black or African American); approximately 19% of subjects were of Hispanic or Latino ethnicity. The mean body weight was 90.6 kg, and the baseline mean body mass index (BMI) was 32.5 kg/m^2 in the randomized population, with the baseline weight and BMI generally similar across treatment groups. More than 61% of the subjects were obese (BMI $\geq$30 kg/m^2) based upon National Institutes of Health criteria with slightly greater representation of obesity in the placebo and canagliflozin 50 mg bid groups than in the canagliflozin 150 mg bid group.

EFFICACY RESULTS

Primary Endpoint: Clinically important reductions in HbA_{1c} at Week 18 relative to placebo were observed with both doses of canagliflozin: LS mean changes from baseline of -0.60% and -0.44% with the 150 mg bid and 50 mg bid canagliflozin doses, respectively ($p<0.001$ for both comparisons), confirming the study's primary hypothesis and key secondary hypothesis, respectively.

Major Secondary Endpoints: All major secondary endpoints of canagliflozin were superior to placebo based on the pre-specified hierarchical testing sequence prespecified in the Statistical Analysis Plan, as illustrated in the tabular summary below.

Change from Baseline to Week 18 LOCF for Primary and Secondary Efficacy Endpoints in Order of Predefined Hierarchical Testing Sequence

(Study 28431754DIA2003: Modified Intent-to-Treat Analysis Set)

	---------- CANA 50 mg bid ---------- (Placebo-Subtracted) -------		---------- CANA 150 mg bid---------- (Placebo-Subtracted) ----------	
Endpoints	Mean (95% CI)	p-value	Mean (95% CI)	p-value
HbA_{1c} Change (%)	-0.44 (-0.637; -0.251)	<0.001	-0.60 (-0.792; -0.407)	<0.001
FPG Change (mmol/L)	-1.31 (-1.820; -0.800)	<0.001	-1.33 (-1.844; -0.826)	<0.001
Body Weight % Change (%)	-2.2 (-3.1; -1.3)	<0.001	-2.6 (-3.5; -1.7)	<0.001
Proportion Achieving <7% HbA_{1c} target	16.3 (1.1; 31.4)	0.013	25.6 (10.6; 40.6)	<0.001

Key: bid=twice daily, CI=confidence interval, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin

Note 1: 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 factor and adjusting for the baseline value as a covariate.

Note 2: For the proportion of patients achieving HbA_{1c} target of <7%, the p-value is based on logistic regression with terms for treatment and stratification factor and adjusting for the baseline value as a covariate.

SAFETY RESULTS:

Adverse Events

The overall incidence of subjects with adverse events for the primary safety analysis was slightly higher in the 150 mg bid canagliflozin group (40.9%) relative to the 50 mg bid canagliflozin group (35.5%) and the placebo group (36.6%). There was a higher incidence of adverse events considered related to study drug on both canagliflozin doses relative to placebo, largely due to adverse events in the Infections and infestations and the Renal and urinary disorders system organ classes (SOCs).

The overall incidence of adverse events leading to discontinuation was low across all groups with a higher incidence in the canagliflozin 150 mg bid group (7.5%) relative to the canagliflozin 50 mg bid group (1.1%) and placebo group (0%). The incidence of serious adverse events was also low across groups, with 3 subjects (3.2%) in the canagliflozin 150 mg bid group, none in the canagliflozin 50 mg bid group, and 1 subject (1.1%) in the placebo group. There was 1 death reported in a subject in the canagliflozin 150 mg bid group. Adverse events of the Infections and infestation SOC were the most frequently reported (ie, >10% of subjects in any treatment group). The overall incidence of adverse events in this SOC was generally similar across treatment groups. Within the SOC, slightly higher incidences of adverse event terms including urinary tract infections and vulvovaginal mycotic infection (and related adverse event terms) were observed in the canagliflozin groups, and slightly higher incidences of nasopharyngitis were reported in the placebo group. There was a higher incidence of drug-related adverse events with canagliflozin treatment, with an incidence of 16.1% and 11.8% in the canagliflozin 150 mg bid and 50 mg bid groups, respectively, and an incidence in placebo of 2.2%. This higher incidence in the canagliflozin groups was mainly due to a higher incidence of specific drug-related adverse events in the Infections and infestations SOC (such as urinary tract infection and vulvovaginal mycotic infection) and in the Renal and urinary disorder SOC (such as pollakiuria) was observed in the canagliflozin groups relative to placebo.

Summary of Treatment-Emergent Adverse Events (Safety)

(Study 28431754DIA2003: Safety Analysis Set)

Number (%) of Subjects with at least one of the following	Placebo (N=93) n (%)	CANA 50 mg bid (N=93) n (%)	CANA150 mg bid (N=93) n (%)	CANA Total (N=186) n (%)
Any adverse events	34 (36.6)	33 (35.5)	38 (40.9)	71 (38.2)
Adverse events leading to discontinuation	0	1 (1.1)	7 (7.5)	8 (4.3)
Adverse events related to study drug[a]	2 (2.2)	11 (11.8)	15 (16.1)	26 (14.0)
Adverse events related to study drug[a] and leading to discontinuation	0	0	5 (5.4)	5 (2.7)
Serious adverse events	1 (1.1)	0	3 (3.2)	3 (1.6)
Serious adverse events leading to discontinuation	0	0	2 (2.2)	2 (1.1)
Serious adverse events related to study drug[a]	0	0	0	0
Serious adverse events related to study drug[a] and leading to discontinuation	0	0	0	0
Deaths	0	0	1 (1.1)	1 (0.5)

[a] Related to study drug includes relationship determined by investigators: possibly related, probably related and very likely related.

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

Safety Laboratory Assessments

A few changes in laboratory safety parameters were observed with canagliflozin 50 mg bid and 150 mg bid groups, including: moderate reductions in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (in the 150 mg bid group), increases in serum bilirubin, creatinine, blood urea nitrogen (BUN), magnesium, and serum phosphate, small decreases in estimated glomerular filtration rate (eGFR), moderate decreases in serum urate, and moderate increases in hemoglobin.

Mean Percent Changes from Baseline at Week 18 for Selected Safety Laboratory Parameters - Within 2 Days of the Last Dose of Study Drug [a]

(Study 28431754DIA2003: Safety Analysis Set)

	% Mean Change from Baseline		
Parameter	Placebo	CANA 50 mg bid	CANA 150 mg bid
Hemoglobin	0.8	5.6	8.0
ALT	1.9	1.7	-7.7
AST	0.7	4.6	-1.2
Serum bilirubin	5.4	7.3	11.1
Serum creatinine	1.4	1.8	4.7
eGFR	-0.3	-0.7	-3.8
BUN	2.0	11.3	14.3
Serum magnesium	0.8	7.2	8.6
Serum phosphate	1.3	5.0	7.9
Serum urate	-0.2	-13.0	-11.2

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

Key: ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, eGFR=estimated glomerular filtration rate

Other Safety Assessments: Treatment with canagliflozin 50 mg bid and 150 mg bid led to modest reductions in blood pressure (systolic reduction greater than diastolic), with minimal changes in pulse rate. These findings were not associated with an increase in reported adverse events of hypotension.

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

CONCLUSIONS:

- ☐ Canagliflozin dosed twice daily, at total daily doses of 100 mg and 300 mg, provides statistically significant glycemic efficacy in add-on use with metformin monotherapy.
- ☐ Additionally, statistically significant reductions in weight and improvements in SBP were observed with both doses of canagliflozin, with improvements in HDL-C observed with the canagliflozin 300 mg total daily dose.
- ☐ Canagliflozin dosed twice daily, at total daily doses of 100 mg and 300 mg, was overall well tolerated, with a modest increase in adverse events of genital mycotic infections in women, a small increase in urinary tract infections in adverse events related to osmotic diuresis, and a low rate of events of hypoglycemia similar to placebo.

Overall, this study met its key primary and secondary hypotheses, suggesting a favorable efficacy, safety, and tolerability profile of both canagliflozin 50 mg bid and 150 mg bid dosing.