SYNOPSIS

Issue Date: 27 April 2012

Document Number: EDMS-ERI-21279836:1.0

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

Protocol No.: 28431754DIA1045

Title of Study: A Double-Blind, Placebo-Controlled, Randomized, Crossover, Multicenter Study to Evaluate the Effect of JNJ-28431754 (canagliflozin) on Post-Meal Glucose in Subjects With Type 2 Diabetes Mellitus

NCT No.: NCT01381887

Clinical Registry No.: CR018373

Principal Investigator: Linda Morrow, MD., Profil Institute for Clinical Research Inc., Chula Vista, California, United States

Study Centers: The study was conducted at 5 centers in the United States: Profil Institute for Clinical Research Inc., Chula Vista, California; Covance Clinical Research Unit, Dallas, Texas; Cetero Research, San Antonio, Texas; Medpace Clinical Pharmacology, Cincinnati, Ohio; Comprehensive Phase One (A Division of Comprehensive NeuroScience, Inc.), Miramar, Florida

Publication (Reference): None

Study Period: 05 July 2011 to 22 November 2011; Database lock date: 12 December 2011

Phase of Development: Phase 1

Objectives:

The primary objectives of the study were to assess the post-meal total plasma glucose area under the curve (PG AUC_{0-2h}) with canagliflozin 300 mg (in the canagliflozin 300 mg/canagliflozin 300 mg treatment) relative to placebo (in the placebo/placebo treatment) administered prior to the meal and to assess the safety and tolerability of canagliflozin.

Key secondary objectives:

Relative to treatment with placebo (canagliflozin 300 mg/placebo treatment) administered prior to a standard meal was to assess:

- the post-meal incremental plasma glucose AUC_{0-2h} with canagliflozin 300 mg (in the canagliflozin 300 mg/canagliflozin 300 mg treatment) administered prior to the meal;
- the post-meal incremental plasma glucose AUC_{0-2h} with canagliflozin 150 mg (in the canagliflozin 300 mg/canagliflozin 150 mg treatment) administered prior to the meal.

Secondary objectives:

Relative to treatment with placebo (placebo/placebo treatment) administered prior to a standard meal was to access:

- the post-meal incremental plasma glucose AUC_{0-2h} (and total and incremental plasma glucose AUC_{0-4h}) with canagliflozin 300 mg (in the canagliflozin 300 mg/canagliflozin 300 mg treatment) administered prior to the meal;
- the post-meal total plasma glucose AUC_{0-2h} (and total and incremental AUC_{0-4h}) with canagliflozin 150 mg (in the canagliflozin 300 mg/canagliflozin 150 mg treatment) administered prior to the meal;
- the plasma insulin and C-peptide AUC_{0-2h}, and total insulin secretion (0 to 2 hours), and the ratios of the insulin and C-peptide AUC_{0-2h}, and total insulin secretion (0 to 2 hours) to the glucose AUC_{0-2h}, with canagliflozin 300 mg (in the canagliflozin 300 mg/canagliflozin 300 mg treatment) administered prior to the meal;
- plasma insulin and C-peptide AUC_{0-2h}, and total insulin secretion (0 to 2 hours), and the ratios of the insulin and C-peptide AUC_{0-2h}, and total insulin secretion (0 to 2 hours) to the glucose AUC_{0-2h}, with canagliflozin 150 mg (in the canagliflozin 300 mg/canagliflozin 150 mg treatment) administered prior to the meal;
- the effect of a single dose of canagliflozin 300 mg (in the canagliflozin 300 mg/canagliflozin 300 mg treatment) on fasting plasma glucose (FPG); and
- the post-meal total and incremental plasma glucagon and glucagon-like peptide-1 (GLP-1) (active and total) AUC_{0-2h} with canagliflozin 150 mg and with canagliflozin 300 mg (ie, canagliflozin 300 mg/canagliflozin 150 mg treatment and the canagliflozin 300 mg/canagliflozin 300 mg treatments, respectively) administered prior to the meal.

Relative to treatment with placebo (canagliflozin 300 mg/placebo treatment) administered prior to a standard meal was to assess:

- the post-meal total AUC_{0-4h} with canagliflozin 300 mg (in the canagliflozin 300 mg/canagliflozin 300 mg treatment) administered prior to the meal;
- the post-meal total AUC_{0-4h} with canagliflozin 150 mg (in the canagliflozin 300 mg/canagliflozin 150 mg treatment) administered prior to the meal;
- the plasma insulin and C-peptide AUC_{0-2h}, and total insulin secretion (AUC_{0-2h}), and the ratios of the insulin and C-peptide AUC_{0-2h}, and total insulin secretion (0 to 2 hours) to the glucose AUC_{0-2h}, with canagliflozin 300 mg (in the canagliflozin 300 mg/canagliflozin 300 mg treatment) administered prior to the meal;
- the plasma insulin and C-peptide AUC_{0-2h}, and total insulin secretion (AUC_{0-2h}), and the ratios of the insulin and C-peptide AUC_{0-2h}, and total insulin secretion (0 to 2 hours) to the glucose AUC_{0-2h}, with canagliflozin 150 mg (in the canagliflozin 300 mg/canagliflozin 150 mg treatment) administered prior to the meal; and
- the post-meal total and incremental plasma glucagon and GLP-1 (active and total) AUC_{0-2h} with canagliflozin 150 mg and with canagliflozin 300 mg (ie, canagliflozin 300 mg/canagliflozin 150 mg treatment and the canagliflozin 300 mg/canagliflozin 300 mg treatments, respectively).

Hypotheses:

Canagliflozin 300 mg (in the canagliflozin 300 mg/canagliflozin 300 mg treatment) administered immediately prior to a standard meal reduces the post-meal total PG AUC_{0-2h} relative to administration of placebo immediately prior to the meal (in the placebo/placebo treatment).

The secondary hypotheses of this study were:

- Canagliflozin 300 mg (in the canagliflozin 300 mg/canagliflozin 300 mg treatment) administered immediately prior to a standard meal reduces the post-meal incremental plasma glucose AUC_{0-2h} relative to administration of placebo (in the canagliflozin 300 mg/placebo treatment) immediately prior to the meal.
- Canagliflozin 150 mg (in the canagliflozin 300 mg/canagliflozin 150 mg treatment) administered immediately prior to a standard meal reduces the incremental glucose AUC_{0-2h} post-meal relative to administration of placebo (in the canagliflozin 300 mg/placebo treatment) immediately prior to the meal.

Methodology: This was a double-blind, placebo-controlled, randomized-sequence, 4-period crossover study. Approximately 36 subjects ≥25 to ≤70 years of age with type 2 diabetes mellitus (T2DM), and with inadequate glycemic control (based upon fasting glucose measurements ≥130 mg/dL and ≤250 mg/dL), and on metformin monotherapy were to be randomized in the study to ensure 30 subjects completed the study. Both subjects on metformin monotherapy and subjects on metformin in dual combination with a sulphonylurea (SU) or a meglitinide or a dipeptidyl peptidase-4 (DPP-4) inhibitor were eligible to be enrolled into the study. The study consisted of 3 phases: pre-treatment, double-blind treatment, and post-treatment. The treatments and sequences evaluated are described in the table below:

Treatment Sequences for Study 2843175DIA1045

Treatment Sequence Group	Period 1	Period 2	Period 3	Period 4
1	A	D	B	C
2	B	A	C	D
3	C	B	D	A
4	D	C	A	B

Treatment A = Placebo/Placebo, Treatment B = Canagliflozin 300 mg/Placebo
Treatment C = Canagliflozin 300 mg/Canagliflozin 300 mg
Treatment D = Canagliflozin 300 mg/Canagliflozin 150 mg

The total study duration of the study was between 12 weeks for subjects who were on metformin monotherapy (during pre-treatment phase) and 16 weeks for subjects who were on a combination therapy consisting of a SU, meglitinide, or DPP-4 inhibitor in addition to metformin or on metformin monotherapy at a dose of <1500 mg per day (during pre-treatment phase).

Randomized subjects received the first dose (1 capsule) of study drug for that treatment period after an overnight fast of at least 8 hours, on the morning of the second day of the 3-day treatment period between approximately 8:00 AM and 9:00 AM, prior to the morning meal. Subjects received the second dose (1 capsule) for that treatment period on the morning of third day of the 3-day treatment period, 20 minutes prior to starting the meal for the mixed meal tolerance test.

Number of Subjects (planned and analyzed): Planned: Thirty-six subjects with T2DM were planned to be enrolled and randomized in the study. Subjects who withdrew were replaced to ensure at least 30 subjects completed the study.

Analyzed: A total of 37 subjects were enrolled and randomly assigned to treatment sequences: 9 subjects each in Sequence ADBC (Sequence 1) and Sequence BACD (Sequence 2), 8 subjects in Sequence CBDA

(Sequence 3), and 11 subjects in Sequence DCAB (Sequence 4). All 37 subjects received at least 1 dose of study drug and were included in the safety analysis set. Thirty-six subjects completed the study. One subject from Sequence 3 was discontinued due to withdrawal of consent.

Diagnosis and Main Criteria for Inclusion: Subjects with T2DM aged ≥25 to ≤70 years of age (inclusive) with inadequate glycemic control (based upon fasting glucose measurements ≥130 mg/dL and ≤250 mg/dL) on metformin monotherapy or a combination therapy consisting of a SU, meglitinide, or DPP-4 inhibitor in addition to metformin or on metformin monotherapy at a dose of <1500 mg per day (during pre-treatment phase).

Test Product, Dose and Mode of Administration, Batch No.: Canagliflozin was supplied for this study as over-encapsulated tablets with 150 mg (50 mg + 100 mg tablet), Batch No. 364729/365113; Bulk Lot No: 11A12/G007, and 300 mg (300 mg tablet), in a gray-colored, hard, gelatin capsule, Batch No. 364730/365114; Bulk Lot No. 30845.14/33977.9.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo capsules consisted of microcrystalline cellulose within a gray-colored, hard, gelatin capsule, Batch No. 364731/365115; Bulk Lot No: 30845.2/30845.13.

Duration of Treatment: The total duration of the study was between 12 weeks for subjects who were on metformin monotherapy (during pre-treatment phase) and 16 weeks for subjects who were on a combination therapy consisting of a SU, meglitinide, or DPP-4 inhibitor in addition to metformin or on metformin monotherapy at a dose of <1500 mg per day (during pre-treatment phase).

Criteria for Evaluation:

Pharmacodynamic/Efficacy Evaluations: The primary efficacy endpoint was the between-treatment difference in total plasma glucose (PG) AUC_{0-2h}. Key secondary efficacy endpoint was the between-treatment differences for incremental PG $AUC_{0-2h.}$

Additional efficacy endpoints of interest included between-treatment differences for the total and incremental AUC_{0-2h} and AUC_{0-4h} for PG, plasma insulin (both absolute and normalized by plasma glucose), and plasma C-peptide (both absolute and normalized by plasma glucose); between-treatment differences for total insulin secretion between 0 to 2 hours and 0 to 4 hours (both absolute and normalized by plasma glucose); between-treatment differences for the total and incremental AUC_{0-2h} for plasma glucagon, and glucagon-like peptide-1(GLP-1 [total and active]); between-treatment differences in 1 and 2 hour post-meal glucose and insulin measurement, and time to peak glucose; and fasting plasma glucose (FPG).

Pharmacogenomic Evaluations: An additional blood sample (10 mL) was collected from subjects who gave separate written informed consent to allow for potential pharmacogenomic research.

Safety and tolerability were evaluated throughout the study based on adverse event monitoring including hypoglycemia, vital signs (blood pressures and pulse rates), body weight, safety laboratory tests (including hematology, chemistry, and urinalysis), and physical examination results.

Statistical Methods:

The inter-subject coefficient of variation (CV) for total PG AUC_{0-2h} was estimated to be less than or equal to 17%. Thus, an intra-subject CV of 15% was assumed for this sample size calculation. With an intra-subject CV of 15% and a 1-sided level of significance of 2.5%, a sample size of 30 completers was sufficient to detect a decrease of 10% between Treatment C and Treatment A with a power of 80%.

The sample size calculation was also based on the data available from previous studies in which the inter-subject CV for the incremental PG AUC_{0-2h} was estimated to be between 30 and 40%. With an intra-subject CV of 30%, and a 1-sided significance level of 2.5%, a sample size of 30 completers was sufficient to detect a decrease of 20% between treatments with a power of 80%. Thirty-six subjects were enrolled in the study to ensure a sample size of 30 completers.

When 12 subjects completed 2 treatment periods, the data were evaluated by an independent, unblinded statistician to estimate the intra-subject CV. The intra-subject CV for total and incremental PG AUC_{0-2h} estimated from the interim evaluation were less than or equal to the ones used for the original sample size calculation. Thus, no adjustments to the study were done based on the interim evaluation.

Pharmacokinetics (PK): Individual and mean canagliflozin plasma concentration-time profiles were plotted for each treatment. Plasma canagliflozin concentration data at each time point and all estimated PK parameters for canagliflozin were summarized with mean, standard deviation (SD), %CV, median, minimum, maximum, and geometric mean (PK parameters only) for each treatment.

Pharmacodynamics (PD):

A mixed-effects model was fitted to the logarithm of total PG AUC_{0-2h}. The ratio and percent difference with corresponding 95% confidence interval (CI) were estimated for pairs of treatments. Hypothesis testing for the equality of mean total PG AUC_{0-2h} between Treatment C and Treatment A was carried out using a 1-sided level of significance of 2.5%.

A mixed-effects model was fitted to the incremental PG AUC_{0-2h}. The difference and percent difference with corresponding 95% CI were estimated for pairs of treatments. Hypothesis testing for the equality of mean total PG AUC_{0-2h} between Treatment C versus Treatment B and Treatment D versus Treatment B was carried out using a 1-sided level of significance of 2.5%.

No adjustments for multiplicity were done.

All other PD parameters were summarized with descriptive statistics.

RESULTS:

STUDY POPULATION: A total of 37 subjects were enrolled and randomly assigned to treatment sequences (9 subjects in Sequence 1, 9 subjects in Sequence 2, 8 subjects in Sequence 3, and 11 subjects in Sequence 4). Thirty-six subjects completed the study. One subject from Sequence 3 was withdrawn due to withdrawal of consent and received only Treatment C.

The median (range) age and BMI of study subjects was 55 (34 to 68) years and 31.2 (23 to 40) kg/m^2, respectively. Twenty-eight subjects were Hispanic or Latino in origin, 7 were non-Hispanic or Latino, and ethnicity for 2 subjects was not reported. There was a higher proportion of men (62%) than women (38%) enrolled in the study.

There were no protocol deviations in this study. All 37 subjects received at least 1 dose of study drug.

PHARMACODYNAMIC RESULTS:

A total of 36 subjects completed the study and were evaluable for the statistical analysis of pharmacodynamics.

A slight reduction from baseline in glycosylated hemoglobin (HbA_{1c}) was observed, consistent with generally stable glycemic control. This supported the assumption regarding the study design of maintaining a stable overall glycemic control during the study. The fasting fingerstick glucose values (measured to assess glucose control prior to each treatment period) were generally similar with no notable

differences between treatment periods, suggesting that stable glycemic control was achieved. In all 3 treatment periods, FPG (obtained prior to the second dose of study medication) was markedly reduced 24 hours after canagliflozin 300 mg relative to Treatment A when placebo was administered. The FPG concentrations prior to the MMTT were highly similar prior to Treatments B, C, and D, indicating that the glucose control prior to each of the test meals was consistent across the treatments.

Incremental and Total Plasma Glucose AUC_{0-2h} and AUC_{0-4h}:

The least squares mean reduction in AUC_{0-2h} of 75 mg·h/dL for Treatment C relative to Treatment A translated into a reduction in the mean PG concentration of approximately 37.5 mg/dL over the 0 to 2 hour interval. Treatment C lowered the incremental PG AUC_{0-2h} (by approximately 12%) relative to Treatment B, confirming the key secondary study hypothesis. This incremental reduction in the incremental glucose excursion, despite generally similar urinary glucose excretion (UGE) (Treatment B relative to Treatment C), indicated that a non-renal mechanism for the decreased glucose excursion with canagliflozin was confirmed. Treatment D (canagliflozin 300 mg/canagliflozin 150 mg) only minimally reduced the incremental PG AUC_{0-2h} relative to Treatment B, with a difference that was not statistically significant.

Similar to the observations over 2 hours, Treatment C lowered the total PG AUC_{0-4h} relative to Treatment A by approximately 17%, and the incremental PG AUC_{0-4h} relative to placebo (ie, Treatment A) by approximately 23%. Treatment C lowered the incremental PG AUC_{0-4h} relative to Treatment B by about 15%, consistent with the reduction observed over 2 hours.

Incremental and Total Plasma Insulin AUC_{0-2h} and AUC_{0-4h}:

Treatment C reduced the total and incremental plasma insulin AUC values both over 2 and 4 hours, relative to Treatments A and B. The ratio of the total and incremental plasma insulin AUC over 2 and 4 hours was assessed, and both ratios were similar for Treatment B relative to Treatment A and both numerically smaller for Treatment C relative to Treatment A.

Incremental and Total Plasma C-Peptide AUC_{0-2h} and AUC_{0-4h}:

Lesser reductions in plasma C-peptide AUC were observed with canagliflozin treatment relative to placebo compared to those observed for plasma insulin AUC. When normalized by plasma glucose (to account for the known effects of glucose to stimulate insulin secretion), no decreases in the ratio of plasma C-peptide AUC to PG AUC were observed with canagliflozin treatment compared to placebo (ie, Treatment A).

Total Insulin Secretion:

Consistent with observations for plasma C-peptide AUC and the ratios of plasma C-peptide AUC to PG, there were only slight numerical reductions in total insulin secretion over 2 and over 4 hours. No notable changes in the ratio of insulin secretion to plasma glucose were observed, although the mean values were always modestly higher with canagliflozin treatment than with placebo treatment (ie, Treatment A).

Incretins and Glucagon: A small increase in total plasma GLP-1 total AUC_{0-2h} was seen for Treatment C relative to Treatment A. For glucagon excursions, a small increase in the total glucagon AUC_{0-2h} was observed for Treatment C relative to Treatment A.

Urinary Glucose Excretion: Minimal UGE was observed with placebo (ie, Treatment A), with generally similar UGE observed over the 0 to 2 hours, 2 to 4 hour, and entire mixed meal tolerance test (MMTT) 0 to 4 hour periods for Treatments B, C, and D. There was a slightly lower UGE with Treatment B relative to Treatment C and Treatment D. Due to small differences in mean UGE_{0-2h} observed between Treatments B, C and D, additional supporting analyses (Test for Equality of Mean UGE_{0-2h} and modeling

of Incremental PG AUC_{0-2h} with UGE_{0-2h} as covariate) were performed. Results also showed that UGE did not alter the extent of reduction or statistical significance of the reduction in incremental PG AUC_{0-2h} with Treatment C relative to Treatment B.

Renal Threshold for Glucose Excretion (RT_G): The mean RT_G in placebo-treated subjects was approximately 240 mg/dL and all canagliflozin treatments substantially reduced RT_G. Consistent with the modestly lower UGE observed with Treatment B compared to Treatment C and Treatment D, a lesser reduction in RT_G for Treatment B was observed compared to Treatment C and Treatment D.

PHARMACOKINETIC RESULTS:

Canagliflozin concentrations observed are consistent with the expected exposures for the doses administered. Mean trough canagliflozin concentrations (measured at -30 minutes on Day 3) were approximately 240-250 ng/mL across the canagliflozin treatment groups. This value was slightly below the estimated 90% maximal effective concentration (EC_{90}) value (292 mg/mL) for the effect of canagliflozin to lower RT_G, but well above the estimated half maximal effective concentration value of 32 ng/mL.

SAFETY RESULTS:

Overall, a similar incidence of adverse events was seen across treatments. The most common adverse events by system order class (SOC) (>10% for any treatment) were observed in the gastrointestinal disorders (27.0%) and nervous system disorders SOC (18.9%). The incidence of specific adverse events was low across treatments, with the only common adverse events (≥5% in any treatment) being diarrhea (18.9%) and headache (13.5%). Only single subjects were reported to have any other particular specific adverse event term, suggesting no discernable pattern. The incidence of the adverse events of diarrhea and headache was not notably different between placebo (ie, Treatment A) and other treatments, where canagliflozin was administered.

All adverse events except 1 were considered as mild in intensity. The moderate intensity adverse event was hypersomnolence in 1 subject, considered as not related to study drug by the investigator. Only 2 adverse events, diarrhea (mild in intensity and considered possibly related) and haematoma (mild in intensity and considered not related) did not resolve during the double-blind treatment period.

A low occurrence of adverse events considered related to study drug was reported, with most considered as possible (including adverse events in the gastrointestinal disorders SOC such as diarrhea) and few considered as probable (including adverse events of decreased appetite and pruritis and pruritis generalized); none of the adverse events considered related to study drug led to any action taken (ie, interruption or discontinuation) with regard to study drug and all were considered as mild in intensity by the investigator.

No meaningful changes in safety laboratory analytes were observed and no clinically relevant changes in blood pressure or heart rate were reported.

No deaths or other serious adverse events were reported during the study. No subject discontinued due to an adverse event.

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

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.