SYNOPSIS

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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.: 28431754DIA1025

Title of Study: An Open-label Study to Compare 2 Methods for Determining the Renal Threshold for Glucose in Subjects With Type 2 Diabetes Mellitus

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Publication (Reference): None

Study Period: 04 January 2011 to 29 July 2011, Database lock: 21 September 2011

Phase of Development: 1

Objectives:

The primary objective of this study was to compare renal threshold for glucose (RT_G) values determined using the new method during a mixed meal tolerance test (MMTT) with the RT_G values determined using the stepwise hyperglycemic clamp method in untreated and canagliflozin-treated subjects with type 2 diabetes mellitus (T2DM).

The secondary objectives of this study were to compare the relationships of blood glucose (BG) and urinary glucose excretion (UGE) rate obtained from the 2 methods (MMTT-based method and stepwise hyperglycemic clamp method) in untreated and canagliflozin-treated subjects with T2DM, and to assess the relationship between RT_G values determined using the 2 methods and canagliflozin plasma concentrations.

Methodology: This was an open-label study, with 2 sequential parts (Part 1 and Part 2).

Part 1:

Part 1 was an exploratory study in subjects with T2DM who were not treated with canagliflozin. In Part 1, the RT_G values for each subject were determined using the MMTT-based method on one day, followed by the stepwise hyperglycemic clamp method on the next day.

Subjects were admitted to the clinical research unit (CRU) in a fasting state, underwent safety assessments, and had a fasting blood sample collected for serum creatinine measurement on the morning of Day -1. Subjects then began a 12-hour urine collection to determine creatinine clearance (CrCl).

On the morning of Day 1, following an overnight fast of at least 8 hours, eligible subjects completed the MMTT. On the morning of Day 2 after an overnight fast of at least 8 hours, subjects underwent the stepwise hyperglycemic clamp procedure (methods detailed below). Blood and urine samples were collected throughout each procedure for analysis of glucose. Subjects received standardized meals from Day -1 to Day 2. Subjects remained domiciled at the CRU until completion of all procedures on Day 2 and were discharged on the same day. A safety follow-up visit was conducted approximately 7 to 10 days after discharge.

Part 2:

Part 2 had a similar study design as Part 1 except that in Part 2, subjects with T2DM were treated with 100-mg canagliflozin once daily for 8 consecutive days for determination of the RT_G values using the 2 methods (MMTT-based method on Day 7; hyperglycemic clamp method on Day 8), and plasma canagliflozin concentrations at steady-state were measured for pharmacokinetics (PK). Preliminary results of RT_G assessments in Part 1 were used to confirm the design and sample size for Part 2.

Subjects were admitted to the CRU on the morning of Day -1 in a fasting state and underwent the same safety and eligibility assessments as performed in Part 1. On Day 1, eligible subjects received their first dose of study drug (1 capsule of 100-mg canagliflozin) with 240 mL of water approximately 10 minutes prior to receiving a standardized breakfast.

Subjects were (1) provided with a glucose meter and testing supplies, instructed on the performance of self-monitored plasma glucose (SMPG) (ie, subjects were required to perform fasting SMPG at least once daily); and counseled on recognition, management, and reporting of hypoglycemia; (2) provided with a protocol-specified diary (for recording of hypoglycemia, SMPG readings, study drug dosing times, and breakfast times); (3) provided with counseling regarding diet and exercise consistent with standard diabetes guidance recommendations, and (4) dispensed study drug (100-mg canagliflozin capsules) for outpatient treatment (1 capsule once daily) on Days 2 to 5. Subjects were instructed not to take their Day 6 study drug at home and to return to the CRU on the morning of Day 6.

Subjects were re-admitted to the CRU on the morning of Day 6 in a fasting condition (ie, for at least 8 hours) and had a fasting blood sample collected for serum creatinine measurement. Subjects then began a 12-hour urine collection to determine CrCl. Subjects received their study drug on Days 6, 7, and 8 with 240 mL of water at the CRU after an overnight fast of at least 8 hours as follows:

- Day 6: approximately 10 minutes prior to receiving a standardized breakfast
- Day 7: approximately 10 minutes prior to starting of the MMTT
- Day 8: at approximately the time when the glycemic target of the first clamp step was achieved

Blood and urine samples were collected throughout each procedure (MMTT-based method and stepwise hyperglycemic clamp method) for analysis of glucose. Blood samples were also collected to measure steady-state plasma canagliflozin concentrations for PK assessments. Subjects remained in the CRU until Day 8 and were discharged on the same day after all study procedures were completed. A safety follow-up visit was conducted approximately 7 to 10 days after discharge.

Number of Subjects (planned and analyzed): Planned: Fourteen subjects were to be enrolled in each Part of the study to ensure that at least 12 subjects would complete RT_G assessments with both methods. Subjects who withdrew were not replaced. A subject could participate in either Part 1 or Part 2, but could not participate in both parts of the study. Analyzed: Twenty-eight subjects with T2DM were enrolled with 14 subjects in Part 1 (untreated subjects) and 14 subjects in Part 2 (canagliflozin-treated subjects); all enrolled subjects completed the study.

Diagnosis and Main Criteria for Inclusion: Men and women aged 18 to 65 years, inclusive, with a body mass index (BMI) between 20 and 39.9 kg/m², inclusive, who had been diagnosed with T2DM for at least 12 months prior to screening (who either had not been receiving any anti-hyperglycemic agents or

had been on a generally stable metformin regimen for at least 12 weeks prior to screening) with a HbA_{1c} of ≥7.0% and ≤10.0% at screening and fasting blood glucose concentrations confirmed between 8 mM (144 mg/dL) and 15 mM (270 mg/dL), at screening and on Day -1 were eligible for enrollment into the study.

Test Product, Dose and Mode of Administration, Batch No.: Canagliflozin was supplied as an over-encapsulated 100-mg tablet in a gray-colored, hard, gelatin capsule (Lot No. ABTK01D; Expiration date: February 2012). The over-encapsulated tablet was backfilled with microcrystalline cellulose to prevent the tablet from rattling in the capsule shell.

During Part 1 of the study, study drug was not administered. During Part 2, subjects received 100-mg canagliflozin once daily on study Days 1 through 8 approximately 10 minutes prior to breakfast. On the outpatient days (Days 2 to 5) subjects self-administered the study drug at home at approximately the same time (10 minutes prior to breakfast) each day. On Days 1, 6, and 7, subjects received 100-mg canagliflozin once daily at the CRU approximately 10 minutes prior to breakfast. On Day 8, subjects were administered study drug approximately when the first clamp target glucose concentration (4 mM) was achieved. Subjects were administered study drug on Days 1, 6, 7, and 8 with 240 mL of water after an overnight fast of at least 8 hours (water was allowed during the fast). Subjects received their study drug at the CRU in the sitting position, and remained sitting until 15 minutes postdose (other than for planned assessments).

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable

Duration of Treatment: The study consisted of a screening phase of up to 21 days to determine eligibility of the subjects, Part 1 which consisted of 2 days assessments (MMTT on Day 1 and stepwise hyperglycemic clamp procedure on Day 2) at the CRU followed by a safety visit after 7 to 10 days, Part 2 which consisted of an 8 day treatment period with canagliflozin 100 mg from Days 1 to 8 along with the assessments on Day 7 for MMTT and Day 8 for stepwise hyperglycemic clamp procedure, and a safety follow up visit after 7 to 10 days.

Criteria for Evaluation:

Pharmacokinetics: Venous blood samples (3 mL each) for determination of canagliflozin plasma concentration were collected. For all subjects in Part 2 of the study, the following PK parameters were determined for canagliflozin based on the individual plasma concentration-time data, using actual sampling times via noncompartmental analysis with validated WinNonlin® (Pharsight Corporation) software: $C_{max\ ss}$, C_{trough}, $t_{max,ss}$, $AUC_{0\text{-}6h,}$ $AUC_{0\text{-}11.5h,}$ $C_{avg0\text{-}6h}$ (MMTT), and $C_{avg0\text{-}11.5h}$ (stepwise hyperglycemic clamp).

Pharmacodynamics: Blood: Venous blood samples (0.2 mL) were collected for measurement of BG during MMTT on Day 1 for Part 1 and Day 7 for Part 2. Blood samples were taken during the hyperglycemic clamp procedure on Day 2 for Part 1 and Day 8 for Part 2.

Urine for Glucose and Creatinine: On Day -1 for Part 1 and Day 6 for Part 2, a 12-hour urine collection was obtained for measurement of urine creatinine. During the MMTT procedure, urine was collected for measurement of glucose from 0 to 2 hours and 2 to 4 hours after receiving the standardized meal. During the hyperglycemic clamp procedure, urine was collected in 2 intervals during each clamp period (0- to 1-hour and 1 to 2.5 hours post start of each clamp step), except that, for the first clamp step, the first urine collection ended when the glycemic target was achieved (t = 0); and the second urine collection started when the glycemic target was achieved (t = 0) and ended at 1.5 hours after the glycemic target was achieved.

The primary PD parameter was RT_G and the secondary PD parameter was the relationship of UGE rate versus BG concentration using the stepwise hyperglycemic clamp method and the MMTT-based method.

Pharmacogenomics: A pharmacogenomic blood sample (10 mL) was collected on Day 1 of both Part 1 and Part 2 of the study from subjects who consented to participate in the optional pharmacogenomics component of the study, as necessary.

Safety: Safety evaluations were based upon the type of incidence and severity of treatment-emergent adverse events (TEAE) (including hypoglycemia) reported throughout the study, physical examinations (including body temperature), vital signs (blood pressures and pulse rates measurements), body weight, 12-lead electrocardiograms (ECG), and clinical laboratory tests (including hematology, serum chemistry, and urinalysis).

Statistical Methods:

Sample size: Based on published data for RT_G determination using the stepwise hyperglycemic clamp technique and using the MMTT-based method in study 28431754 NAP1002, the intrasubject coefficient of variation (CV) of RT_G was assumed to be 15% for this sample size calculation. With an intrasubject CV of 15% for RT_G, a sample size of 12 completers for each group (untreated and treated subjects with T2DM) was estimated to be sufficient for the estimated mean RT_G from MMTT to fall within 89% and 112% of the mean of the clamp method, with 90% confidence.

Pharmacokinetic Analyses: Individual and mean canagliflozin plasma concentration-time profiles were plotted for each treatment. For canagliflozin plasma concentrations at each sampling time and for all PK parameters descriptive statistics, including arithmetic mean, standard deviation (SD), CV, geometric mean, median, minimum, and maximum were calculated.

Pharmacodynamic Analyses: Using a mixed effects model appropriate for the design with RT_G as the dependent variable, means and intrasubject SD were estimated. The RT_G values were log-transformed before the analysis and geometric means were calculated for the 2 methods. The ratio of the 2 geometric means along with the 90% confidence interval (CI) for the ratio was reported. The 2 methods of calculating RT_G were considered similar if the 90% CI fell within the (0.8, 1.25) boundary.

A linear regression model was fitted to the data with RT_G from MMTT as the dependent variable and RT_G from the clamp method as the predictor to estimate the intercept and slope of the model. Pearson correlation coefficient and concordance correlation coefficient between RT_G from the 2 methods were calculated. The concordance coefficient could also be used to judge closeness between the 2 methods. If the concordance coefficient is at least 0.7, the 2 methods can be considered similar.

Because a fairly small range of RT_G values were observed in Part 1 and a similarly small range was expected in Part 2, the correlation and concordance analysis was specified to be done for the combined data set (both Part 1 and Part 2) in addition to being done within each Part separately. The combined analysis was pre-specified because of the inherent limitations associated with identifying correlations between 2 measurements when the range of observed values is of a similar magnitude as the precision of the measurements (in this case, the precision is limited in part by the size of the hyperglycemic clamp steps being 45 mg/dL apart).

A secondary objective of the study was to evaluate the relationship between UGE rate and BG. For this, the UGE rate versus BG relationship was evaluated using graphical techniques.

Safety Analyses: All subjects were included in the safety and tolerability analyses. Baseline values (for all laboratory and safety evaluations, vital signs, and 12-lead ECG measurements) were defined as the last evaluation on Day -1. Laboratory data were summarized by the type of laboratory test. Descriptive statistics were calculated for each laboratory analyte at baseline and at each scheduled timepoint and changes from baseline were summarized by laboratory test parameter and timepoint. A listing of subjects with any laboratory results outside the reference ranges was provided. Electrocardiogram measurements were summarized at each timepoint of measurement and change from baseline was summarized by parameter and timepoint, vital signs were analyzed descriptively and the changes from baseline at each scheduled timepoint were summarized, and results of physical examination were listed.

RESULTS:

STUDY POPULATION:

A total of 28 subjects with T2DM were enrolled with 14 subjects in Part 1 (untreated subjects) and 14 subjects in Part 2 (canagliflozin-treated subjects). All enrolled subjects completed the study. No imbalances in demographic characteristics were noted between Part 1 and Part 2. Overall a higher proportion of men were enrolled in each Part of the study; however, the distribution by gender within each Part was identical. All subjects were white and the median age was similar in Part 1 (56.5 years) and Part 2 (57.5 years). The mean body weight, BMI, and estimated glomerular filtration rate (eGFR) were similar in Part 1 and Part 2 of the study. Mean baseline HbA_{1c} values were comparable between Part 1 and Part 2 (8.3% and 8.0%, respectively); however, more subjects with HbA_{1c} ≤8.5% at screening were enrolled in Part 2 (86% of subjects) compared with subjects enrolled in Part 1 (50% of subjects). Mean baseline (Day -1) fasting serum glucose values were comparable between Part 1 and Part 2 (10.8 mmol/L and 11.2 mmol/L, respectively).

PHARMACOKINETIC RESULTS: After repeated once daily 100 mg doses of canagliflozin (Days 1 to 8) in Part 2, trough plasma canagliflozin concentrations achieved apparent steady-state by Day 6. Mean $C_{max,ss}$, $C_{avg0-6h}$, and AUC_{0-6h} values for canagliflozin at steady-state were similar on Day 7 and Day 8. The median $t_{max,ss}$ for canagliflozin was slightly longer on Day 7 compared to Day 8.

PHARMACODYNAMIC RESULTS: A 5-step hyperglycemic clamp procedure was performed to determine the relationship between BG concentrations and UGE rate over the range of BG concentrations commonly observed in subjects with T2DM. The relationship between BG and UGE rate was well-described by a threshold-like relationship in both untreated and canagliflozin-treated subjects, with values of RT_G much lower in canagliflozin-treated subjects than in untreated subjects (geometric LS mean RT_G = 215 mg/dL in untreated subjects and 43.1 mg/dL in canagliflozin-treated subjects).

Good agreement was obtained between RT_G values obtained from the hyperglycemic clamp procedure (RT_G^{clamp}) and RT_G values obtained using the new MMTT-based method (RT_G^{MMTT}). The MMTT-based method requires an estimate of GFR. When using MDRD-eGFR to determine RT_G^{MMTT}, mean RT_G values were similar between the 2 methods in both untreated (geometric mean ratio [GMR] = 0.925) and canagliflozin-treated subjects (GMR = 1.033). In addition, the RT_G^{MMTT} and the RT_G^{clamp} values were highly correlated when using the RT_G data combined from Part 1 in untreated subjects and Part 2 in canagliflozin-treated subjects. With the combined RT_G data, the concordance correlation coefficient was 0.94 when using the MDRD-eGFR, and was 0.88 when using the 12-hour measured CrCl to estimate GFR, both well above the pre-specified acceptance criterion of 0.7. Better agreement between RT_G^{clamp} and RT_G^{MMTT} was obtained when using MDRD-eGFR to calculate RT_G^{MMTT} than when using 12-hour measured CrCl to estimate GFR.

SAFETY RESULTS: Overall, all study procedures and drug treatments were generally well tolerated in Part 1 (untreated) and Part 2 (canagliflozin-treated). There were no discontinuations due to adverse events. One subject in Part 2 reported a serious adverse event of abdominal pain 8 days after the last dose of study drug which was considered by the investigator as doubtfully related to study drug. A higher incidence of adverse events was reported in Part 2 (11 subjects [78.6%]) than in Part 1 (2 subjects, [14.3%], mainly due to pollakiuria and/or polyuria reported in 8 subjects (4 men and 4 women) in Part 2 and no subjects in Part 1. These pollakiuria and/or polyuria adverse events were mild, self-limited, and did not lead to discontinuation. The adverse events assessed by the investigator as possibly related to the study drug were pollakiuria, polyuria, pruritis, and vulvovaginal mycotic infection. One subject in Part 2 reported 1 episode of hypoglycemia accompanied with mild dizziness and tremor on Day 3, with recovery after ingestion of carbohydrates. Plasma glucose levels measured by glucometer were 74 mg/dL and 108 mg/dL at the beginning and the end of the episode, respectively.

No laboratory test results were reported as adverse events, and no clinically meaningful mean or individual subject changes (shifts) in laboratory analytes from baseline to end-of-study were observed. No clinically relevant changes were observed in vital signs, physical examinations, or ECG parameters.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor

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