SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Name of Finished Product	Canagliflozin
Name of Active Ingredient(s)	JNJ-28431754

Protocol No.: JNJ-28431754DIA1007

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of JNJ-28431754 in Type-2 Diabetes Mellitus Subjects not Optimally Controlled (HbA1c: ≥7.0%) on Fixed Doses of Insulin Therapy

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Publication (Reference): None

Study Period: 27 MAY 2008 to 05 MARCH 2009; DBL 06 APRIL 2009

Phase of Development: Phase 1

Objectives: The primary objective was to assess the safety and tolerability of JNJ-28431754 (canagliflozin) after multiple oral doses in subjects with type-2 diabetes mellitus (T2DM) on fixed doses of insulin therapy. Secondary objectives were to (1) evaluate the pharmacodynamic (PD) effects including, plasma glucose, urine glucose excretion (UGE), and glycosylated hemoglobin (HbA1c) of canagliflozin relative to placebo, and (2) assess pharmacokinetic (PK) exposure, explore exposure-response relationships, and to develop a population PK model. Exploratory objectives were to explore: (1) the changes in intestinal hormone secretion during a mixed meal tolerance test (MMTT) relative to placebo; (2) evaluate SGLT1 activity by assessing changes in hydrogen breath test values relative to placebo; and (3) assess changes in gastric emptying rate (using acetaminophen as a standard) relative to placebo.

Methodology: This was a randomized, double-blind, placebo-controlled, multiple-dose, parallel-group study conducted at 2 study centers to evaluate the safety, PK, and PD of canagliflozin over a 4-week treatment period in T2DM subjects not optimally controlled on fixed doses of insulin therapy. Two parallel cohorts of subjects were studied, with 1 dose level of canagliflozin evaluated in each cohort. The study consisted of 6 phases: (1) a screening phase (Days -52 to -32); (2) an optional run-in phase (Days -31 to -18); (3) a stabilization phase (2 weeks duration; Days -17 to -4); (4) a baseline phase (Days -4 to -1); (5) a 4-week double-blind treatment phase during which subjects were to be domiciled at the study center on Days 1, 2, and 24 to 29; and (6) a 1.5 week end-of-study phase.

Number of Subjects (planned and analyzed): Planned: Amendment INT-1 changed the study design from 3 cohorts to 2 cohorts (ie, dropped planned 300 mg qd dose) and the number of subjects to be enrolled was decreased from 42 to 28 subjects. Twenty-eight subjects were to be enrolled to ensure that at least 26 subjects would complete all required assessments. Ten subjects were to be randomized to each of 2 drug treatment Cohorts (ie, Cohort 1, canagliflozin 100 mg once daily [qd] and Cohort 2, canagliflozin 300 mg twice daily [bid]), and 4 subjects were to be randomized to receive matching placebo within each Cohort. Analyzed: 29 subjects were enrolled and 27 subjects completed the study. All subjects who received at least 1 dose of the study drug were included in the safety and tolerability analyses; PD analyses were performed on all subjects who received at least one dose of canagliflozin or placebo and had at least 1 PD assessment; and PK analyses were performed on all subjects who received at least 1 dose of active study drug (canagliflozin or acetaminophen).

Diagnosis and Main Criteria for Inclusion: Men and women between 18 and 65 years of age, inclusive, with a BMI between 25 and 45 kg/m², inclusive, with T2DM (for at least 6 months) who were receiving fixed doses of insulin for at least 2 weeks, and who were not optimally controlled on insulin as determined by HbA1c (%) levels (HbA1c ≥7.0% and ≤10.5%), and who met all other protocol inclusion and exclusion

criteria, were eligible for enrollment. Women were either postmenopausal, surgically sterile, or if sexually active, practicing an effective method of birth control.

Test Product, Dose and Mode of Administration, Batch No.: Test Drug: canagliflozin; supplied as overencapsulated tablets to provide active dose strengths of 100 mg (Lot #PD2779; expiration December 2008) and 300 mg (Lot #PD2783; expiration July 2009). Doses of canagliflozin administered orally were 100 mg qd and 300 mg bid. Acetaminophen (1,000 mg) was supplied as Tylenol extra strength adult liquid (500 mg in 15 mL) by the study center and was from the same lot number for all subjects.

Reference Therapy, Dose and Mode of Administration, Batch No.: Matching placebo capsules (Lot #PD2776; expiration dates December 2008, January 2009, and December 2012) were used as the reference in each treatment Cohort.

Duration of Treatment: Eligible subjects randomized to double-blind treatment received either canagliflozin or placebo for 28 consecutive days. Overall study duration was approximately 13 weeks.

Criteria for Evaluation: Blood samples were collected for PK and PD (plasma glucose, HbA1c) and urine samples for PD (UGE) and for safety.

Pharmacokinetics: Venous blood samples (3 mL each) for PK analyses were collected predose on Days 1, 7, 14, 21, and 27 and up to 24 hours postdose on Day 28 and on Day 29 (48 hours after the last dose) for determination of canagliflozin. Plasma samples were analyzed to determine concentrations of canagliflozin using a validated, specific and sensitive liquid chromatography coupled to mass spectrometry/mass spectrometry (LC-MS/MS) method at PRA International (Assen, The Netherlands) under the supervision of the Sponsor's bioanalytical department. The quantification range for canagliflozin was 5.0 ng/mL to 5,000 ng/mL. PK parameters estimated from plasma data included: C_{max}, C_{trough}, $t_{max,}$ AUC_{last}, $AUC_{0\text{-}10hr}$ (300 mg bid only), $AUC_{10\text{-}24h}$ (300 mg bid only), $AUC_{0\text{-}24h}$, $t_{1/2}$, λ_z, and CL_{ss}/F for canagliflozin.

Venous blood samples (2 mL each) for determination of acetaminophen plasma concentrations were collected on Days -3 and 25. Plasma samples were analyzed to determine concentrations of acetaminophen using a validated HPLC-UV method at PRA International (Assen, The Netherlands) under the supervision of the Sponsor's bioanalytical department**.** The quantification range was 0.50 to 50.0 µg/mL for acetaminophen. Pharmacokinetic parameters estimated from plasma data included: C_{max}, t_{max}, AUC_{last}, $AUC_{0\text{-}12h}$, AUC_{∞}, $t_{1/2}$, and λ_z for acetaminophen.

Pharmacodynamic Evaluations:

UGE: UGE (grams of glucose) was measured for each 24-hour collection interval on Days -1, 1, and 27. UGE rate was calculated as the amount of glucose excreted per hour (UGE_h), and as the cumulative amount of glucose excreted over each 24-hour period (UGE_{24h}).

Plasma Glucose: Mean 24-hour plasma glucose concentration was calculated on Days -1, 1, and 27 as the area under the plasma glucose concentration-time curve over 0 to 24 hours, divided by 24 hours (ie, glucose $AUC_{0\text{-}24h/24}$). Postprandial glucose excursions were calculated as the area under the plasma glucose concentration-time curve from 0 to 4.5 hours post-dose (ie, $AUC_{0\text{-}4.5h}$). FPG was determined at each scheduled timepoint and change from baseline (Day -1) calculated.

HbA1c: For each dose group and placebo, HbA1c (%) and changes from baseline (Day -3) were summarized with descriptive statistics at Day 27.

Renal Threshold for Glucose ($RT_{glucose}$): $RT_{glucose}$ was estimated on Days -1, 1, and 27 as a function of time for each subject based on measured plasma glucose, UGE, and estimated glomerular filtration rate (eGFR). Two measures of $RT_{glucose}$ were reported for each subject: (1) the 24-hour mean value and (2) the value in the overnight period (13-24 hours after dosing). The 24-hour mean $RT_{glucose}$ was calculated over each of the 3 time intervals (0 to 4.5 hours), (4.5 to 10.5 hours), and (10.5 to 24 hours). The 24-hour mean value for each subject was calculated as the weighted mean of the $RT_{glucose}$ values calculated over each of these intervals.

Exploratory evaluations:

Acetaminophen absorption test (evaluation of gastric emptying): A single oral dose of acetaminophen (1,000 mg as Tylenol extra strength adult liquid, [500 mg in 15 mL]) was administered on the morning of Days -3 and 25, 10 minutes prior to breakfast at the same time of administration of the double-blind study drug (canagliflozin or placebo) after an overnight fast of at least 8 hours. Blood samples were collected and processed for determination of plasma acetaminophen.

Hydrogen Breath Test (evaluate glucose malabsorption): A hydrogen breath test was conducted on Days -2 and 26 to explore possible effect of canagliflozin on intestinal SGLT1 activity. Subjects were administered 75 g of anhydrous glucose in 225 mL of water in the sitting position after an overnight fast. Breath samples were collected at baseline and at 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, and 120 minutes after ingestion of the glucose load. Breath hydrogen and methane concentrations were measured and expressed in parts-per-million (ppm). An increase of at least 10 ppm within a 2-hour period was indicative of bacterial overgrowth or glucose malabsorption.

Intestinal Hormone Secretion during MMTT: The standardized mixed meal tolerance test (MMTT) was conducted on Day -1 (baseline) and Day 27 to explore the effects of canagliflozin on intestinal hormone secretion. On Day -1 and Day 27, blood samples (6 mL) were collected at 30, 60, 90, and 120 minutes post-MMTT for determination of total and active glucagon-like peptide-1 (GLP-1) and total peptide-YY (PYY). For total and active GLP-1 and total PYY, the area under the concentration-time curve over 0 to 2 hours (AUC_{0-2h}) postdose was calculated on Days -1 and 27.

Pharmacogenomics: An optional pharmacogenomic blood sample (10 mL) was collected at screening (Day –1) to allow for pharmacogenomic research, as necessary.

Safety Evaluations: Safety and tolerability were evaluated throughout the study using spontaneous adverse event reporting, clinical laboratory tests (serum chemistry, hematology, urinalysis); electrocardiograms (ECGs); vital sign measurements; physical examinations and anthropometric measurements; severe and serious hypoglycemic episodes, assessment of renal glomerular function and markers of proximal renal tubular function; pregnancy tests; assessment of calcium and phosphate homeostasis, bone turnover markers, and hormones regulating calcium and phosphorus homeostasis.

Statistical Methods:

Sample Size Determination: Using an estimated intersubject coefficient of variation of 35% for AUC_{0-24h} and C_{max} of canagliflozin at steady-state, a sample size of 10 subjects was determined to be sufficient for the point estimate of the geometric mean AUC_{0-24h} and C_{max} of canagliflozin at steady-state, to fall within 77.9% and 128.4% of the true value with 95% confidence. Using an estimated intersubject CV of 35% for the UGE_{24hr} change from baseline after multiple dosing of canagliflozin, a sample size of 10 subjects was determined to be sufficient for the point estimate of the arithmetic mean UGE_{24h} change from baseline to fall within 75% and 125% of the true value with 95% confidence. Twenty-eight subjects were to be enrolled in the study to ensure that at least 26 subjects completed all required assessments. Fourteen subjects were to be enrolled in each treatment Cohort to ensure that at least 13 subjects completed each dose level. Within each Cohort, if the number of subjects dropped below 13, additional subjects were enrolled to ensure that at least 13 subjects completed each treatment Cohort. Unless otherwise noted, data were summarized for each dose level and the placebo data from each Cohort were grouped together.

Pharmacokinetic analyses: Data for all subjects that received at least 1 dose of active study drug (ie, canagliflozin or acetaminophen) were included in the PK analysis set. Plasma concentrations and PK parameters for canagliflozin and acetaminophen were summarized and descriptive statistics were generated for each dose group. Predose (trough) plasma concentrations of canagliflozin (C_{trough}) on Days 7, 14, 21, and 27 were expressed graphically to evaluate attainment of steady-state.

Pharmacodynamic analyses: PD analyses were performed on all subjects that received at least 1 dose of canagliflozin or placebo and with at least 1 PD assessment. PD parameters were summarized with descriptive statistics at each scheduled time-point for each treatment group and placebo.

24-Hour UGE: UGE_{24h} and UGE_{24h} changes from baseline (Day -1) were summarized for each dose group and for placebo, with descriptive statistics at each scheduled timepoint. The difference in mean UGE_{24h} change from baseline between each dose and placebo were estimated using an analysis of variance model with associated 90% CIs. An ANCOVA model that included UGE_{24h} change from baseline as the dependant variable and UGE_{24h} at baseline as a covariate and treatment (each canagliflozin dose level and placebo) as fixed effects were used to estimate the least-squares (L-S) means and intersubject variance. Using estimated L-S means and intersubject variance, the point estimate and 90% CIs for the difference in means between canagliflozin and placebo were estimated.

Plasma Glucose: Individual and mean 24-hour plasma glucose concentration-time profiles on Days -1, 1, and 27 were summarized using descriptive statistics and displayed graphically for each dose group and for placebo. Glucose $AUC_{0-24hr/24}$, postprandial glucose excursions ($AUC_{0-4.5h}$), and fasting plasma glucose were summarized with descriptive statistics at each scheduled timepoint. The effects of

canagliflozin on plasma glucose relative to placebo were summarized with descriptive statistics and the difference in mean changes from baseline between each dose and placebo was estimated together with associated 90% CI for the differences in means.

HbA1c: HbA1c (%) with changes from baseline (Day -3) were summarized with descriptive statistics at each scheduled timepoint. The difference in mean change of HbA1c (%) from baseline between each dose and placebo was summarized using descriptive statistics together with associated 90% CIs for the difference in means.

Exploratory analyses: Statistical analyses were performed to evaluate the effects of canagliflozin versus placebo on gastric emptying (acetaminophen absorption), carbohydrate malabsorption (hydrogen breath test), and intestinal hormone secretion (during a MMTT).

Acetaminophen absorption: The effect of canagliflozin on gastric emptying was evaluated using the rate of acetaminophen absorption with and without coadministration of canagliflozin. The primary parameters of interest for the statistical analysis were the log-transformed estimated AUCs (AUC_{∞}, $AUC_{0\text{-}24h}$) and C_{max} of acetaminophen. Only data from subjects who completed both Day -3 and Day 25, and were randomized to canagliflozin, were included in the statistical analysis. The ratio of mean PK parameters (AUCs and C_{max} of acetaminophen with and without co-administration of canagliflozin) was constructed using the estimated least-squares means and intrasubject variance from a mixed effects model. The limits of the CIs were retransformed using antilogarithms to obtain 90% CIs for the ratios of the mean AUCs and C_{max} of acetaminophen with (Day 25) and without co-administration of canagliflozin (Day -3). The ratio of median t_{max} values of acetaminophen, with and without co-administration of canagliflozin, together with an associated 90% CI, was estimated using nonparametric methods.

Hydrogen Breath Test (evaluation of glucose malabsorption): For each group, breath hydrogen and methane concentrations together with changes from baseline (Day -2) were summarized with descriptive statistics at each scheduled timepoint. The difference in mean change from baseline in breath hydrogen and methane concentrations between each dose and placebo were estimated together with associated 90% CIs for the difference in means.

Effect on Intestinal Hormone Secretion During a MMTT: For each group, $AUC_{0\text{-}2h}$ for total and active GLP-1 and $AUC_{0\text{-}2h}$ for total PYY together with changes from baseline (Day -1), were summarized with descriptive statistics at each scheduled time-point. The difference in mean change from baseline in $AUC_{0\text{-}2hr}$ for total and active GLP-1 and $AUC_{0\text{-}2hr}$ for total PYY between each dose and placebo was estimated together with associated 90% CIs for the difference in means.

Safety analyses: Subjects randomly assigned to double-blind treatment who received at least 1 dose of the study drug were included in the safety analyses. Safety was evaluated by examining the incidence of adverse events (including symptomatic hypoglycemia), changes in clinical laboratory test values, physical examination results, 12-lead ECGs, vital signs measurements, 7-point SMBG, urinalysis and markers of renal tubular function, calcium and phosphate homeostasis, bone turnover markers, and hormones regulating calcium and phosphorus homeostasis assessments from the screening phase through study completion. Baseline for all laboratory evaluations, renal safety parameters, and 12-lead ECG measurements was defined as the last evaluation done before the first study drug administration. For vital signs and anthropometric evaluations, baseline was the average of corresponding scheduled time points on Days -3, -2 and -1.

RESULTS: Overall, 27 of 29 (93%) randomized subjects completed the study, including all subjects in the canagliflozin groups and 7 of 9 (78%) subjects in the placebo group. Reasons for early withdrawal of 2 subjects in the placebo group were withdrawal of consent (1 subject) and family emergency (1 subject). Demographic and baseline characteristics of enrolled subjects were generally similar among treatment groups with the exception of the following differences: (1) a lower median age (41.5 yrs) in the canagliflozin 300 mg bid group compared to canagliflozin 100 mg qd group (50.5 yrs) and placebo (52 yrs); (2) a greater number of male subjects in the canagliflozin 100 mg qd group (70%) compared to canagliflozin 300 mg bid group (30%) and placebo (56%); (3) a higher mean body weight in the canagliflozin 100 mg qd group (107.8 kg) compared to canagliflozin 300 mg bid group (94.1 kg) and placebo (95.1 kg); and (4) a lower mean 24-hour plasma glucose ($AUC_{0\text{-}24hr/24}$) in canagliflozin 100 mg qd group (167.5 mg/dL) compared to canagliflozin 300 mg bid (203.3 mg/dL) and placebo (181.8 mg/dL). At baseline all 29 enrolled subjects were stably managed on insulin therapy and 12 (41%) of 29 subjects were additionally taking metformin. The type of insulin and metformin use was similar across groups. Whereas, the mean total daily insulin dose was similar in placebo and canagliflozin 300 mg bid groups, the insulin

dose was nearly twice as much in the canagliflozin 100 mg qd group (114.6 units/day versus 51.4 units/day in the canagliflozin 300 mg bid group and 38.4 units/day in the placebo group). No protocol deviations were reported.

PHARMACOKINETIC RESULTS: Canagliflozin was rapidly absorbed and maximum plasma canagliflozin concentrations on Day 27 were reached within 2.75 to 4.0 hours of dosing. Plasma canagliflozin steady-state conditions were achieved within 7 days for both doses. C_{max} (100 mg qd: 773±213 ng/mL; 300 mg bid: 3556 ±945 ng/mL) and AUC (100 mg qd: 5957 ±1580 h.ng/mL; 300 mg bid: 42308 ±6461 h.ng/mL) increased with increasing dose and terminal half-life (100 mg qd: 14.7 ±4.1h; 300 mg bid: 11.8±2.9 h) was independent of dose.

PHARMACODYNAMIC RESULTS:

24-Hour plasma glucose: Following both single and multiple oral doses of canagliflozin, mean glucose concentrations were lowered throughout the day compared to baseline, and were relatively unchanged in the placebo group. Compared to placebo at Day 27, mean $AUC_{0\text{-}24h/24}$ plasma glucose was significantly decreased from baseline in the 100 mg qd canagliflozin group (Geometric Mean Ratio = 0.81, 95%CI [0.688; 0.945] and 300 mg bid canagliflozin group (Geometric Mean Ratio = 0.82; 95%CI [0.696; 0.974]).

24-Hour UGE: UGE_{24h} increased dose dependently from baseline (Day -1) after both single (ie, Day 1) and multiple doses (ie, Day 27) of canagliflozin. On Day 27, the L-S mean change in UGE_{24h} from baseline between each canagliflozin treatment and placebo was 67.2 g ($p<0.001$; 90% CI 39.6; 94.8) for 100 mg qd and 153.6 g ($p<0.001$; 90% CI 125.2; 181.9) for 300 mg bid. The observed mean (SD) change of UGE_{24h} from baseline was 71.9 (33.8) g and 129.2 (65.9 g on Day 27 for canagliflozin 100 mg qd and 300 mg bid, respectively compared to -3.2 (15.6) g on Day 27 for the placebo group.

$RT_{glucose}$**:** Compared to placebo in which $RT_{glucose}$ remained unchanged from Day -1 to Day 27, in canagliflozin 100 mg qd and 300 mg bid groups, mean [SD] $RT_{glucose}$ decreased on Day 1, with a greater decrease noted in the 300 mg bid group ($RT_{glucose}$ = 99 [30] mg/dL). On Day 27, $RT_{glucose}$ was reduced to a similar level as seen on Day 1 in the canagliflozin 100 mg qd group. In the canagliflozin 300 mg bid group, the mean [SD] reduction in $RT_{glucose}$ was greater on Day 27 (77 [22] mg/dL) than on Day 1 (99 [30)] mg/dL).

FPG: On Day 27 (predose), the L-S mean change (SE) in FPG from baseline versus placebo was -42.7 (14.8) mg/dL and -44.6 (15.1) mg/dL for canagliflozin 100 mg qd and 300 mg bid, respectively. FPG was reduced to a similar extent by both canagliflozin doses and the changes were statistically significant versus placebo. On Day 27, the observed mean (SD) changes in FPG from baseline were -38.1 (22.7) mg/dL and -42.4 (28.6) mg/dL for canagliflozin 100 mg qd and 300 mg bid, respectively, compared to 8.7 (41.2) mg/dL for the placebo group.

HbA1c (%): Consistent with the observed reductions in FPG, on Day 27 (predose) mean HbA1c was dose dependently decreased from baseline (Day -3) by canagliflozin compared to placebo. L-S mean reductions of HbA1c from baseline on Day 27 versus placebo were -0.37 ($p = 0.097$) and -0.55 ($p = 0.019$) for canagliflozin 100 mg qd and 300 mg bid, respectively. On Day 27, the observed mean (SD) changes in HbA1c from baseline were -0.73 (0.50) and -0.92 (0.66) for canagliflozin 100 mg qd and 300 mg bid, respectively, compared to -0.19 (0.49) for placebo.

EXPLORATORY RESULTS:

Acetaminophen absorption test: Following 100 mg qd or 300 mg bid oral administration of canagliflozin or placebo for 25 days, acetaminophen concentration-time profiles and pharmacokinetic parameters were similar compared to acetaminophen alone (baseline, Day -3), indicating that canagliflozin at the doses tested did not alter gastric emptying.

Hydrogen breath test: No consistent increases of hydrogen breath test values on Day 26 were observed in canagliflozin groups and maximum values did not exceed the cut-off of 10 ppm during the 2-hour time period of the test. These data indicate that treatment with canagliflozin for 26 days at doses of 100 mg qd and 300 mg bid was not associated with carbohydrate malabsorption.

Post-MMTT plasma glucose and intestinal hormone secretion: At doses up to 300 mg bid, canagliflozin did not significantly affect post-prandial glucose excursions (ie, no significant effect on incremental plasma glucose increases from premeal levels) or postprandial excursions of intestinal hormones (total and active GLP-1, and total PYY). However, due to the small sample size and high variability, interpretation of the data was not deemed reliable.

PHARMACOGENOMIC RESULTS: No subject withdrew consent for pharmacogenomic research and no genes were genotyped in this study.

SAFETY RESULTS: No deaths and no treatment-emergent SAEs were reported and no subjects discontinued from the study due to adverse events (AEs). Overall, a total of 25 (86%) subjects experienced at least 1 treatment-emergent AE (TEAE) and the overall incidence was similar across groups, with 9 and 8 subjects in the canagliflozin 100 mg qd and 300 mg bid groups, respectively, compared to 8 subjects in the placebo group. Most common TEAEs reported in at least 20% of subjects overall were nervous system disorders (48%), gastrointestinal disorders (41%), musculoskeletal and connective tissue disorders (24%), and respiratory, thoracic and mediastinal disorders (21%). General disorders and administration site conditions, and injury, poisoning and procedural complications were each reported in 14% of subjects overall. Diarrhea, headache, and nasal congestion were more commonly reported in the 300 mg bid canagliflozin group relative to placebo and 100 mg qd canagliflozin groups. No symptomatic genital infections, major adverse cardiovascular events, fractures or venous thromboembolic events were reported. All TEAEs were considered by the investigator to be mild or moderate in severity and no subjects were assessed by the investigators with TEAEs classified as probably related or very likely related to study drug. TEAEs not resolved at the last study visit were reported in 3 subjects (worsening of hypertriglyceridemia, generalized contact dermatitis and headache); all other TEAEs were resolved at the end of the study. Overall, 12 subjects across the 3 groups experienced at least 1 treatment-emergent symptomatic hypoglycemic episode, with 6 subjects in the canagliflozin 100 mg qd group, 3 subjects in the canagliflozion 300 mg bid group, and 3 subjects in the placebo group. None of the hypoglycemic episodes were classified as severe or serious and no subjects discontinued from the study due to symptomatic hypoglycemia. No subjects had their insulin dose reduced due to a symptomatic hypoglycemic event. One subject in the placebo group had an increase in insulin dose due to hyperglycemia.

Other than the analytes discussed below, no consistent changes from baseline in laboratory chemistries or hematology analytes relative to placebo were seen in canagliflozin groups. Mean urinary pH decreased slightly from baseline at Day 27 in canagliflozin groups, without apparent dose-dependency, compared to placebo. Urine osmolality increased in both canagliflozin groups relative to placebo with a greater increase noted in the 300 mg bid canagliflozin group.

Of the bone turnover markers (serum osteocalcin, urinary N-telopeptide [uNTX], urinary deoxypyridinoline [DPD]), hormones regulating calcium and phosphorous homeostasis (ie, 1,25-dihydroxy vitamin D, or PTH), and mineral balance (serum and urinary calcium, magnesium, phosphate, and the fractional excretion rate for calcium, magnesium, and phosphate) monitored during the study, there were no trends or consistent changes noted in canagliflozin treatment groups compared to placebo.

Changes in markers of renal glomerular function noted in subjects treated with canagliflozin compared to placebo included the following. BUN and serum creatinine tended to increase from baseline (Day -1) at Day 27 in a non-dose-related manner in canagliflozin groups compared to placebo with values appearing to return to baseline with discontinuation of treatment. Creatinine clearance and calculated glomerular filtration rate tended to decrease from baseline (Day -1) at Day 27 in a non-dose-dependent manner relative to placebo with values appearing to return to baseline with discontinuation of treatment.

Assessment of renal tubular function did not reveal any clinical relevant changes induced by canagliflozin treatment other than a transient increase in urinary sodium excretion and urinary fractional excretion of sodium on Day 1 of treatment. This effect on sodium was not seen at Day 27 or the end-of-study visit. Urine albumin, beta-2-microglobulin, potassium, chloride, magnesium, and phosphate, and the fractional excretion rate of potassium, chloride, magnesium, and phosphate were not consistently changed over time in canagliflozin groups compared to placebo. On Day 1 of treatment, urinary N-acetyl-beta-d-glucosaminidase (NAG) excretion tended to increase from baseline in a non dose dependent fashion in canagliflozin groups relative to placebo. At Day 27, urinary NAG returned to baseline levels in the canagliflozion groups. Urinary urate was decreased from baseline at Day 27 in a dose related manner in canagliflozin groups compared to placebo. The observed mean (SD) change in urinary urate from baseline on Day 27 was -93.8 (385.5) mg and -212.8 (656.1) mg in the canagliflozin 100 mg qd and 300 mg bid groups, respectively, compared to 48.0 (86.6) mg for the placebo group.

No new clinically significant physical examination abnormalities were noted during the study. Consistent with urinary loss of calories as glucose, canagliflozin yielded greater mean (90% CIs) reductions in body weight (BW) from baseline at Day 27 compared to no change in BW in the placebo group [ie, -0.76 kg (90%CI -1.44; -0.08) and -1.2 kg (90%CI -2.21; -0.23) for 100 mg qd and 300 mg bid, respectively].

Canagliflozin treatment tended to be associated with modest reductions from baseline in standing and supine systolic (SBP) and diastolic blood pressure (DBP) and an increase in standing pulse at Day 27 compared to placebo, without causing an increase in symptoms due to orthostatic hypotension.

No clinically relevant changes in HR or ECG measurements (ie, PR, QRS, QT and QTc intervals) were noted in canagliflozin treatment groups compared to placebo. No abnormal mean values for QTcB or QTcF were observed for any treatment group.

Overall, no new, unusual, or unexpected safety signals associated with canagliflozin treatment were detected in this study.

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

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