SYNOPSIS

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

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; or Janssen Research & Development, LLC. The term "sponsor" is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved

Date: 17 September 2012

Prepared by: Janssen Research & Development, LLC

Protocol No.: 28431754DIA1047

Title of Study: A Double-Blind, Placebo-Controlled, Randomized, Parallel-Groups Study to Investigate the Effects of JNJ-28431754 (Canagliflozin) on Plasma Volume and Renal Function in Subjects With Type 2 Diabetes Mellitus

EudraCT Number: 2011-004117-17

NCT No.: NCT01483781

Clinical Registry No.: CR100685

Principal Investigator: [redacted]

Study Center(s): 1 study center: [redacted]

Publication (Reference): None

Study Period: 23 December 2011 to 07 August 2012. Database lock date: 24 August 2012

Phase of Development: Phase 1

Objectives: The primary objectives were (1) to assess the effect of canagliflozin 300 mg/day relative to placebo on plasma volume (PV) after 12 weeks of treatment and (2) to assess the safety and tolerability of canagliflozin.

Secondary objectives were to assess the effect of canagliflozin 300 mg/day relative to placebo on (1) plasma volume after 1 week of treatment, (2) urine volume after 1 and 12 weeks of treatment, (3) body weight after 1 and 12 weeks of treatment, (4) 24-hour fractional and total excretion of uric acid after 1 and 12 weeks of treatment, (5) urine pH after 1 and 12 weeks of treatment, and (6) HbA_{1c} after 12 weeks of treatment.

Methodology: This was a double-blind, placebo-controlled, randomized, parallel-groups study conducted in subjects between ages 25 to70 years (inclusive) with T2DM with inadequate glycemic control on metformin monotherapy, and on therapy with an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). Approximately 40 subjects were planned to be enrolled. Subjects were randomly assigned to canagliflozin 300 mg or placebo treatment in a 1:1 ratio.

The study consisted of 3 phases: (1) pre-treatment, (2) double-blind treatment, and (3) post-treatment.

1) Pre-Treatment Phase

For subjects on metformin monotherapy (at a dose ≥1,500mg/day) for at least 8 weeks prior to Screening:

- Screening Visit (Week -3)
- Single-Blind Placebo Run-In Period (Days -14 to -4; Starting at Week -2 visit)
- Single-Blind Placebo Baseline Period (Days -3 to 1 predose)

For subjects on metformin and another antihyperglycemic agent (AHA) (either a sulphonylurea [SU] or meglitinide or a dipeptidyl peptidase 4 [DPP-4] inhibitor), or on metformin at a dose <1,500 mg/day prior to Screening:

- Screening Visit (Week -8)
- Metformin Dose Regimen Stabilization Period Starting Visit (Week -7)
- Metformin Dose Regimen Stabilization Period Telephone Contact or Visit (Week -5)
- Single-Blind Placebo Run-In Period (Days -14 to -4; Starting at Week -2 visit)
- Single-Blind Placebo Baseline Period (Day -3 to Day 1 predose)

2) Double-Blind Treatment Phase

- Double-blind study drug treatment started on Day 1 and ended on Day 85 (approximately 12 weeks later), or at an end-of-treatment visit for any subject prematurely discontinuing the Double-Blind Treatment Period.

3) Post-Treatment (Follow-Up) Phase

A follow-up visit was to be completed 7 to 10 days after the last dose of the double-blind study drug.

Number of Subjects (planned and analyzed): Planned: Approximately 40 subjects with T2DM were planned to be enrolled to ensure that at least 17 subjects per treatment group would complete the study. Analyzed: A total of 59 subjects were screened and 36 subjects meeting the entrance criteria were randomized into the study, with 18 subjects each in the canagliflozin 300 mg and placebo groups. Of the 36 subjects randomized, 35 subjects completed the study. One subject was discontinued due to a benzodiazepines positive drug test on Day 1.

Diagnosis and Main Criteria for Inclusion: Men and women 25 to 70 years of age, inclusive, with a diagnosis of T2DM for at least 3 months prior to screening and on a stable regimen (for at least 4 weeks prior to screening) of an ACEI or ARB who met 1 of the following 3 criteria at Screening were eligible for inclusion in the study: (1) on metformin monotherapy at a stable dose of ≥1,500 mg per day for at least 8 weeks prior to Screening with a glycosylated hemoglobin (HbA_{1c}) of ≥7.0% and ≤9.0% at Screening, or (2) on metformin monotherapy at a stable dose of <1,500 mg per day for at least 8 weeks prior to Screening with an HbA_{1c} of ≥7.5% and ≤9.5% at Screening, or (3) on dual combination of metformin (at a stable dose of ≤1,500 mg per day for at least 8 weeks prior to Screening) and a SU or meglitinide or DPP-4 inhibitor (eg, sitagliptin, saxagliptin, or vildagliptin) with an HbA_{1c} of ≥6.5% and ≤8.5% at Screening. Eligible subjects were to have fasting plasma glucose (FPG) ≤225 mg/dL (12.5 mM) at the Week -2 visit. Subjects were ineligible for the study if they met any of the following key criteria: (1) had a history of diabetic ketoacidosis, T1DM, or diabetes secondary to pancreatitis or pancreatectomy; (2) had history of brittle or labile diabetes control; (3) had proliferative diabetic retinopathy, history of clinically significant, symptomatic peripheral diabetic neuropathy; (4) had 1 or more severe hypoglycemic episodes within 6 months before screening; (5) history of hereditary glucose-galactose

malabsorption or primary renal glycosuria; (6) were receiving a PPARγ agonist (eg, a thiazolidinedione (TZD) [pioglitazone or rosiglitazone]), ongoing insulin therapy, another SGLT2 inhibitor, or any other AHA (including agents such as colesevelam and bromocriptine within 12 weeks before the screening visit; (7) had a body mass index <23 kg/m^2 or >38 kg/m^2; (8) had an ongoing eating disorder, had significant weight loss or weight gain or had taken a weight loss medication within 12 weeks before the screening visit; (9) had renal disease, or a history of dialysis or renal transplant; (10) had history of myocardial infarction, unstable angina, pulmonary hypertension, revascularization procedure or cerebrovascular accident within 6 months before screening; (11) had a history of orthostatic hypotension; (12) had taken any antihypertensive medication other than ACEIs or ARBs (eg, diuretics, calcium channel blockers, beta blockers, alpha adrenergic blockers) within 4 weeks prior to the screening visit; and (13) estimated glomerular filtration rate (eGFR) <70 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease Study equation, or serum creatinine ≥1.2 mg/dL (106 µmol/L) for men and ≥1.1 mg/dL (97 µmol/L) for women at Screening and at Week -2 (for subjects undergoing the AHA washout period only).

Test Product, Dose and Mode of Administration, Batch No.: Canagliflozin capsules containing active 300 mg tablets (Bulk Lot No. 32783.2) for oral administration.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo capsules matching canagliflozin capsules in appearance (size and color) (Bulk Lot No. 32580.4) for oral administration.

Duration of Treatment: The study duration was to be approximately 17 weeks for subjects on metformin monotherapy (dose ≥1,500 mg/day) at study entry, and up to a maximum of approximately 22 weeks for subjects requiring AHA washout (ie, washout of an SU or meglitinide or a DPP-4 inhibitor) and/or metformin dose regimen stabilization. Double-blind study drug treatment started on Day 1 and ended on Day 85 (approximately 12 weeks later), or at an end-of treatment visit for any subject prematurely discontinuing the Double-Blind Treatment Period. A follow-up visit was to be completed 7 to 10 days after the last dose of the double-blind study drug.

Criteria for Evaluation:

Pharmacodynamic: The primary pharmacodynamic (PD) endpoint as specified in the Statistical Analysis Plan (SAP) was an estimate of the difference between canagliflozin 300 mg/day and placebo as the mean percent change from baseline (Day 1, predose) in PV at Week 1 and Week 12. Additional PD evaluations performed at Week 1 and Week 12 included: body weight (BW), 24-hour urinary volume, 24-hour fractional and 24 hour total excretion of uric acid, urine pH, and HbA_{1c} (%) (at Week 12 only). The change from baseline at Week 1 and Week 12 for other PD endpoints of interest included: hematocrit, serum creatinine, eGFR, blood urea nitrogen (BUN), BUN/creatinine ratio, 24-hour fractional and 24-hour total excretion of sodium and potassium, 24-hour urinary glucose excretion (UGE), fasting plasma glucose (FPG), and supine and standing blood pressures (BPs).

Pharmacokinetics: Venous blood samples (4 mL each) were collected from all subjects during the double-blind treatment phase for determination of canagliflozin in plasma at predetermined time points. For all subjects, based on the individual plasma concentration-time data, using actual sampling times, the following steady-state plasma pharmacokinetic (PK) parameters of canagliflozin were determined: $C_{max,ss}$, $t_{max,ss}$, $AUC_{\tau,ss}$, and C_{trough}.

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

Safety: Safety and tolerability were evaluated throughout the study based on adverse event monitoring, including hypoglycemia, routine clinical safety laboratory tests (including chemistry, hematology, and urinalysis), 12-lead electrocardiograms (ECGs), vital sign measurements (BP and pulse rates), BW, and physical examination results at pre-specified time points.

Statistical Methods: The estimated sample size for this study was based on published studies that have assessed the variability for repeated PV determinations using the indocyanine green (ICG) indicator dye dilution method in humans. The estimated SD of the percent change from baseline in repeated measurements of PV was reported as ≤6%. However, the variability for repeated PV measurements in the published studies may be underestimated due to differences in study design (eg, the time interval between the serial PV test-retest, with or without experimental interventions conducted between the two repeat PV measurements, or study population). Therefore, a higher SD (8%) for the percent change from baseline in PV measurements than the reported 6% was used for estimating the sample size for the present study. Assuming an SD of 8% for the percent change from baseline in PV determinations, a sample size of 17 completers per treatment group would be sufficient to estimate the difference in mean percent change from baseline between canagliflozin 300 mg and placebo to within ± 5.6% with 95% confidence. In addition, this sample size would be adequate for detecting a difference in mean percent change from baseline in PV between canagliflozin and placebo groups of 8% with at least 80% power and 2.5% 1-sided level of significance, an effect size similar to that reported for mild thiazide diuretics.

An initial analysis was performed to assess the SD of percent change from baseline, by an independent, unblinded statistician, based on repeated PV measurement data from subjects who received placebo among the first 12 subjects completing study procedures through Day 9. The estimated SD of percent change from baseline in repeated PV obtained from this analysis was used to re-evaluate whether the planned sample size per protocol was adequate for the primary study endpoint. The estimated SD was 4.2%. This estimate was lower than those assumed in the original sample size estimation. Based on this interim estimate of SD, assuming the same variance of 4.2% for canagliflozin and placebo groups, a sample size of 6 completers per treatment group would be sufficient to estimate the difference in mean percent change from baseline between canagliflozin 300 mg and placebo to within ±5.4% with 95% confidence. In addition, this sample size would be adequate for detecting a difference in mean percent change from baseline in PV between canagliflozin and placebo groups of 8% with at least 84% power and 2.5% one-sided level of significance. No change to sample size was made based on the initial estimation of SD. The same analysis was performed based on repeated PV measurement data from 18 subjects who received placebo among all randomized subjects completing through Day 9. The estimated SD of percent change from baseline in repeated PV obtained from this analysis was 12%. However, despite the modestly larger variability for repeated PV measurements, it was deemed that the existing sample size still enabled estimation of treatment effect with adequate precision, and no change to sample size was considered necessary.

Pharmacodynamic Analyses: Plasma volume was measured using a validated, non-radioactive, ICG indicator dilution method. $PV = D/C_0$, where D is the dose of ICG injected, and C_0 is the theoretical plasma ICG concentration at t = 0. For each PV measurement, ICG (0.25 mg/kg) was intravenously injected. Blood samples were collected every 30 seconds from 2 to 5 minutes after the end of injection for measurement of the ICG concentrations. The theoretical initial plasma ICG concentration (ICG_0) was estimated by fitting the measured ICG concentrations to a monoexponential decay and then back-extrapolating the fit to either t=0 (Method 1) or t=1 (Method 2) to obtain ICG_0. The back-extrapolation method designated Method 2 was used as the primary analysis method for estimating the initial ICG concentrations, as defined in the SAP. For all PD parameters, a mixed effect model was fitted to estimate the 95% CI for the difference in LS means between canagliflozin and placebo groups at Week 1 and Week 12.

The PD analysis set included all available PD data from randomized subjects who received at least 1 dose of double-blind study drug. For the comparison/estimation on change from baseline between treatments at Week 1 and Week 12, only subjects who had PD values at both baseline and post-baseline (Week 1 and Week 12, respectively) were included. The primary statistical analysis was an estimate of the difference between canagliflozin 300 mg/day and placebo as the mean percent change from baseline in PV at Week 1 and Week 12. The PD endpoints of interest in the comparison between canagliflozin 300 mg and placebo as specified the SAP are shown below.

Pharmacodynamic Endpoints for Comparison Between Canagliflozin 300 mg and Placebo

Endpoint	Analysis[a]	Comment
Percent change from baseline for Plasma Volume at Weeks 1 and 12	Estimation	Primary endpoint
Change from baseline for Plasma Volume at Weeks 1 and 12	Estimation	Secondary endpoint
Change from baseline for Plasma Volume (weight normalized) at Weeks 1 and 12	Estimation	Secondary endpoint
Percent change from baseline for Plasma Volume (weight normalized) at Weeks 1 and 12	Estimation	Secondary endpoint
Change and % change from baseline for Body Weight at Weeks 1 and 12, respectively	Estimation	Secondary endpoint
Change from baseline for 24-hour Urinary Volume at Weeks 1 and 12, respectively	Estimation	Secondary endpoint
Change from baseline for 24-hour Fractional and Total Excretion of Uric Acid at Weeks 1 and 12, respectively	Estimation	Secondary endpoint
Change from baseline for Urine pH at Weeks 1 and 12, respectively	Estimation	Secondary endpoint
Change from baseline for HbA_{1c} (%) at Week 12	Estimation	Secondary endpoint
Change from baseline for other pharmacodynamic endpoints of interest[b] at Weeks 1 and 12, respectively	Estimation	Secondary endpoint

[a] 95% confidence intervals were produced for the differences between treatments.
[b] Other pharmacodynamic endpoints of interest included hematocrit, eGFR, serum creatinine, BUN, BUN/creatinine ratio, 24-hour fractional and total excretion of sodium and potassium, and 24-hour UGE, FPG, and blood pressure.

Pharmacokinetic Analyses: Individual subject and mean canagliflozin plasma concentration-time profiles were plotted for each treatment. Plasma concentrations of canagliflozin at each sampling time and PK parameters were summarized using descriptive statistics, including arithmetic mean, median, minimum, maximum, standard deviation (SD), coefficient of variation, and geometric mean.

Safety Analyses: All subjects who received at least 1 dose of double-blind study drug were included in the safety and tolerability analyses. The overall incidence (ie, number and percent of subjects with 1 or more adverse events in each category) of adverse events, serious adverse events, adverse events leading to discontinuation, were summarized by treatment group. Adverse events by system organ class (SOC) (the number and the percentage of subjects with one or more adverse events within a SOC) were summarized by treatment group. The incidence of adverse events (by preferred term, grouped by SOC, and presented by treatment group) were also summarized by severity (by each designation, mild, moderate, or severe) and by the relationship (not related, doubtful, possible, probable, or very likely) to study drug. Adverse events for which subjects had their treatment discontinued, and serious or persistent adverse events were listed, if applicable, by treatment, SOC, and dictionary-derived term. Hypoglycemia events reported as adverse events/serious adverse events were summarized by treatment group, where applicable. Adverse events which were defined in the protocol as requiring the collection of additional information and additional analysis included: urinary tract infection, vulvovaginitis in women, and genital infections in men. Descriptive statistics for the additional information collected for these adverse events, where applicable, were summarized by treatment group. Laboratory data were summarized by the type of laboratory test. Descriptive statistics were calculated for each laboratory analyte at baseline and at each

scheduled time point and changes from baseline were summarized by laboratory test parameter and time point. The number and percentage of subjects with specific treatment-emergent laboratory values meeting the predefined limit of change (PDLC) criteria were summarized for these laboratory analytes and a corresponding listing was provided. The preplanned criteria for PDLC values were defined in the SAP. Electrocardiogram measurements were summarized at each time point of measurement and change from baseline was summarized by parameter and time point, vital signs were analyzed descriptively and the changes from baseline at each scheduled time point were summarized, and results of physical examination were listed.

RESULTS:

STUDY POPULATION: A total of 59 subjects were screened and 36 subjects were randomized to treatment, with 18 subjects each in the canagliflozin 300 mg and placebo groups. Among the 36 subjects randomized, 35 subjects completed the study. One subject (Subject [redacted]) was discontinued due to a drug test that was positive for benzodiazepines on Day 1, which became available to the investigator only after the Day 1 study drug dosing and completion of the Day 1 PV procedures. The subject was discontinued from the study on Day 1.

Subject randomization was stratified by metformin dose stabilization requirement (ie, already stabilized or required a stabilization period). Most subjects randomized were already on a stable, protocol-specific dose of metformin monotherapy, with 9 (25%) subjects requiring modification of their regimen to be eligible for the study. The number of subjects who required the metformin dose stabilization period was similar between treatment groups.

The demographic and baseline disease characteristics were consistent with the study protocol inclusion and exclusion criteria and were generally similar between the 2 treatment groups. All 36 subjects were white and the majority of subjects (86%) were men. Subjects ranged in age from 51 to 71 years with a median age of 63 years. Approximately half the subjects were obese (ie, BMI ≥30 kg/m^2). The overall mean (SD) baseline BW was 93.5 (14.43) kg, the mean (SD) duration of diabetes was 8.5 (4.11) years, and the mean (SD) baseline HbA_{1c} was 7.7 (0.54) %. The mean (SD) baseline eGFR was 90.8 (14.88) and 103.8 (14.94) mL/min/1.73 m^2 for the canagliflozin and placebo treatment groups, respectively, ranging from 71 to 132 mL/min/1.73 m^2 across the treatment groups. The mean baseline standing and supine systolic and diastolic BPs were similar between the treatment groups.

There were no protocol deviations in the study. All 36 subjects received at least 1 dose of study drug.

EFFICACY RESULTS: There were no primary or secondary efficacy endpoints defined for this study. Results of pharmacodynamic endpoints measured at Week 1 and Week 12 are described under Pharmacodynamic Results.

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:

PHARMACOKINETIC RESULTS:

The steady-state canagliflozin concentrations achieved and PK parameters assessed on Day 7 and Day 85 were consistent with the expected exposures after multiple-dose administration of 300 mg canagliflozin based on historical data. Mean trough (C_{trough}) canagliflozin concentrations (measured at predose on Day 7 and Day 85) were 313 ng/mL and 303 ng/mL, respectively. The mean (SD) steady-state plasma canagliflozin PK parameters on Day 85 are presented in the table below.

Arithmetic Mean (SD) Steady-State Canagliflozin Plasma Pharmacokinetic Parameters on Day 85
(Study 28431754DIA1047: Pharmacokinetic Analysis Set)

Parameter	300 mg Canagliflozin
N	17
$C_{max,ss}$ (ng/mL)	3863 (1082)
$t_{max,ss}$ (h)[a]	1.00 (1.00-2.00)
$AUC_{\tau,ss}$ (ng.h/mL)	20824 (5057)

[a] Median (range)

PHARMACODYNAMIC RESULTS: A total of 35 subjects completed the study and were evaluable for the statistical analysis of pharmacodynamics.

Plasma Volume: The primary PD endpoint for this study was the between treatment difference in mean percent change from baseline in PV. The mean PV values at baseline were comparable in the canagliflozin (3.22 L) and placebo (3.28 L) groups. At Week 1, in the canagliflozin group, the LS mean percent change in PV from baseline was -5.4% and was 4.3% in the placebo group, for a between group difference of -9.7%, with the 95% CI around the between-group difference excluding "0". At Week 12, in both groups, increases in LS mean percent change from baseline were observed, with an attenuated between-group difference of -1.2%, with the 95% CI around the between-group difference including "0". Overall, a similar trend was observed for the percent change from baseline over time in BW-normalized PV for canagliflozin treatment relative to placebo, as compared with the non-BW-normalized PV results.

Other PD Endpoints:

24-hour urinary glucose excretion: Treatment with canagliflozin led to a sustained increase in UGE over the 12 weeks: a rise from baseline by about 509 mmol (92 g) and 459 mmol (83 g) at Week 1 and Week 12, respectively; no meaningful changes from baseline in UGE were observed with placebo treatment.

24-hour urine volume: In the canagliflozin group, a mean increase from baseline of approximately 270 mL/24 hours was observed at Week 1, with a smaller mean increase of approximately 150 mL/24 hours observed at Week 12. In the placebo group, small increases in mean 24-hour urine volume (approximately 100 mL/24 hours) were observed at Weeks 1 and 12. The 95% CI around the between-group differences at both Weeks 1 and 12 included "0".

Body weight: After 1 week of treatment, a small reduction in mean BW was observed in the placebo group, with a larger reduction observed in the canagliflozin group, so that the between-group difference in the LS mean change from baseline was -1.35 kg. After 12 weeks of treatment, a small mean increase from baseline in BW in the placebo group was observed, with a continued reduction from baseline in the canagliflozin group, so that the between-group difference in LS mean change from baseline was -3.47 kg, with the 95% CI around the between-group difference excluding "0".

Measures of Renal Function:

- *eGFR:* In the canagliflozin group, a decrease in eGFR from baseline was observed, by 2.52 and 2.15 mL/min/1.73m^2 at Weeks 1 and 12, respectively, (approximately 3% decreases at both time points). In the placebo group, small increases in eGFR from baseline at Weeks 1 and 12 were observed. Comparison of the LS mean changes from baseline in eGFR values showed 95% CIs around the between-treatment differences that included "0" at Weeks 1 and 12.
- *BUN and BUN/Creatinine Ratio:* In the canagliflozin group, the mean change from baseline in BUN was approximately 23% and 27% at Weeks 1 and 12, respectively, with minimal changes from baseline at both time points in the placebo group. Comparison of the LS mean changes from baseline in BUN showed 95% CIs around the between-treatment differences that excluded "0" at Week 1 and

Week 12. An increase in mean BUN/creatinine ratio from baseline (approximately 20%) was observed in the canagliflozin group at both Week 1 and Week 12, with minimal changes observed in the placebo group.

- *24-Hour total (TE_{Na}) and fractional excretion of sodium (FE_{Na}):* There were no meaningful changes from baseline at Weeks 1 and 12 in serum sodium concentration with either treatment. Increases in TE_{Na} were seen in both treatment groups that were only slightly greater with canagliflozin relative to placebo at Weeks 1 and 12, with the 95% CI around the between-group difference including "0" at both time points. In the canagliflozin group, FE_{Na} did not notably change at Week 1, with an increase from baseline of 0.13% seen at Week 12 (about a 17% increase). No discernible change in FE_{Na} was observed in the placebo group at either time point. Comparison of the LS mean changes from baseline in 24-hour FE_{Na} showed 95% CIs around the between-treatment differences which excluded "0" at Week 12.

- *24-Hour total (TE_K) and fractional excretion of potassium (FE_K):* There were no meaningful changes from baseline at Weeks 1 and 12 in serum potassium concentration with either treatment. Modest increases in TE_K from baseline were seen at Weeks 1 and 12 in both treatment groups, only slightly greater with canagliflozin, with the 95% CIs around the between-treatment differences including "0" at both time points. In the canagliflozin group, the mean change from baseline in FE_K was less than 1% at Week 1 and about 2% (approximately a 19% increase) at Week 12. Only minimal changes in FE_K were seen in the placebo group at either time point. Comparison of the LS mean changes from baseline in FE_K showed 95% CIs around the between-treatment differences which excluded "0" at Week 12.

- *24-Hour total (TE_{UA}) and fractional excretion of uric acid (FE_{UA}):* Mean serum uric levels at baseline were approximately 340 and 353 µmol/L in the canagliflozin and placebo groups, respectively. Canagliflozin decreased the mean serum uric acid concentration from baseline by approximately 50 and 32 µmol/L at Week 1 and Week 12, respectively, with no discernible changes in the placebo group. At Week 1, canagliflozin increased mean TE_{UA} from baseline by about 0.4 and 0.3 mmol at Week 1 and Week 12. A small increase in TE_{UA} was also observed in the placebo group. Overall, the mean increases in TE_{UA} from baseline observed at Week 1 and Week 12 with canagliflozin relative to placebo were approximately 8% and 5%, respectively. The 95% CI around the between-treatment differences at both time points included "0". At Week 1 and Week 12, slight decreases in FE_{UA} were seen in the placebo group, with small increases in FE_{UA} in canagliflozin group, with similar between-treatment differences (approximately 2%) observed at both time points, with the 95% CI around the between-group differences at both time points including "0".

- *Urine pH:* Reductions from baseline in mean urine pH were observed in both treatment groups at Weeks 1 and 12, with larger decreases seen in the canagliflozin treatment group. At Week 12, only a small between-treatment difference in the LS mean change from baseline was observed (-0.10 pH units), with the 95% CI around this difference including "0".

- *Hematocrit:* In the canagliflozin group, a mean increase in hematocrit from baseline of approximately 0.5% was observed at Week 1 (an increase of approximately 1%) and by approximately 2.4% (an increase of approximately 6%) at Week 12, which then returned towards baseline in follow-up 7-10 days after the last dose of study drug. Minimal changes from baseline in hematocrit at Weeks 1 and 12 were observed in the placebo group. Comparison of the LS mean changes from baseline in hematocrit showed 95% CIs around the between-treatment difference that excluded "0" at Week 12.

Vital Signs:

- *Systolic BP:* Canagliflozin treatment lowered the mean supine SBP from baseline by approximately 10 mmHg at Week 1 and by approximately 11 mmHg at Week 12. Placebo treatment did not meaningfully change supine SBP at Week 1 or Week 12. Comparison of the LS mean changes from baseline in supine SBP showed 95% CIs around the between-treatment differences that excluded "0"

at Weeks 1 and 12. Canagliflozin treatment lowered the mean standing SBP from baseline by approximately 11 mmHg at Week 1 and by approximately 15 mmHg at Week 12. In the placebo group, mean standing SBP was reduced from baseline by approximately 3 mmHg at Week 1 and was was not changed at Week 12. Comparison of the LS mean changes from baseline in standing SBP showed 95% CIs around the between-treatment differences that excluded "0" at Week 12. No notable differences from baseline in the standing-supine SBP were observed at Week 1 or Week 12.

- *Diastolic BP:* Modest reductions from baseline in mean supine DBP were observed at Week 1 (approximately -2.8 mmHg) and Week 12 (approximately -4.9 mmHg) with canagliflozin treatment. No meaningful change from baseline in mean supine DBP was observed at Week 1 or Week 12 with placebo treatment. Comparison of the LS mean changes from baseline in supine DBP showed 95% CIs around the between-treatment differences that excluded "0" at Week 12. Modest reductions from baseline in mean standing DBP were observed at Week 1 (-4.0 mmHg) and at Week 12 (approximately -5.7 mmHg) with canagliflozin treatment. No meaningful changes from baseline in standing DBP were observed at Week 1 or Week 12 with placebo treatment. Comparison of the LS mean changes from baseline in DBP showed 95% CIs around the between-treatment differences that excluded "0" at Week 12. No notable changes from baseline in the standing-supine DBP were observed at either time point.
- *Pulse Rate:* No meaningful change from baseline in mean supine pulse rate was observed in either treatment group at Weeks 1 and 12. A small increase from baseline in mean standing pulse rate (by about 4 bpm) was observed at Week 1 in the canagliflozin treatment group; this increase in the mean standing pulse rate was not observed at Week 12. There were no notable changes in standing pulse rate in the placebo group.

Glycemic Endpoints:

- *HbA_{1c}:* Mean HbA_{1c} at Week 12 was reduced with canagliflozin treatment compared to placebo treatment: the LS mean change from baseline was -0.61% with 95% CIs around the between-treatment differences that excluded "0".
- *Fasting plasma glucose:* Canagliflozin treatment lowered mean FPG at both Week 1 and Week 12 (placebo-subtracted LS means of -1.05 mmol/L (-18.9 mg/dL) and -1.60 mmol/L (-28.8 mg/dL), respectively), with the 95% CI around the between-treatment difference in the LS mean changes from baseline excluding "0" at both time points.

PHARMACOGENOMIC RESULTS: No subject withdrew consent for pharmacogenomics research and no genes were genotyped.

SAFETY RESULTS: The population evaluable for safety included all randomized subjects who received at least 1 dose of study drug and provided post-baseline safety data.

Adverse events: Overall, 50% of subjects reported at least 1 adverse event, with a higher percentage in the canagliflozin group (61%) than in the placebo group (39%). The most common adverse events (>10% of subjects in any treatment group) by SOC were observed in the Gastrointestinal disorders and in the Infections and infestations SOCs. Three adverse events were reported in more than a single subject in the canagliflozin group, diarrhea (in 4 subjects), nasopharyngitis (in 3 subjects), and myalgia (in 2 subjects), with all 3 events reported less frequently in the placebo group (1, 2, and 0 subjects, respectively). All adverse events were considered by the investigator to be mild to moderate in intensity, none led to discontinuation of study drug, and all events were resolved during the double blind treatment period.

Two vulvovaginal adverse events (vulvovaginal mycotic infection and vulvovaginal pruritus) and 1 adverse event of balanoposthitis (uncircumcised) were reported in the canagliflozin group. The investigator assessed the vulvovaginal events as mild in intensity and either probably related to study drug (vulvovaginal mycotic infection) or not related to study drug (vulvovaginal pruritus). The adverse event of balanoposthitis was assessed by the investigator as moderate in intensity and possibly related to study

drug. One adverse event of transient dizziness postural (assessed by the investigator as mild in intensity and possibly related to study drug) was reported in the canagliflozin group.

No deaths were reported, no subject discontinued from the study due to an adverse event, and no adverse event of hypoglycemia was reported. One serious adverse event was reported; Subject [redacted], [redacted] in the canagliflozin group, was hospitalized on Day 103 (18 days after the last dose of study drug) for an elective surgery (tympanoplasty) for the treatment of right tympanic membrane perforation; the perforation occurred on Day 28 (related to a bout of sneezing). The investigator considered the serious adverse event of moderate intensity and not related to the study drug.

Safety Laboratory Assessments: Generally, small differences relative to placebo in the canagliflozin group were observed in mean changes from baseline over time. Small mean decreases in alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, and alkaline phosphatase were observed in the canagliflozin group, with small increases in these analytes in the placebo group. A moderate increase from baseline in serum magnesium and phosphate was observed with canagliflozin, as compared with minimal or no changes in the placebo group. No meaningful changes from baseline were observed in other serum electrolytes, including serum chloride, calcium, potassium, or sodium. A moderate mean decrease from baseline in serum urate was observed at Week 12 with canagliflozin compared to a mean increase in the placebo group. A small increase from baseline in hemoglobin was observed at Week 12 in the canagliflozin group, with commensurate increases in blood erythrocytes and hematocrit, which then returned towards baseline at follow-up, 7 to10 days after the last dose of study drug; these parameters were minimally changed in the placebo group. No clinically meaningful changes in other hematology parameters were observed. No meaningful changes from baseline in routine dipstick urinalysis parameters (specific gravity, pH) were observed.

Other safety assessments: Canagliflozin lowered supine and standing blood pressures with minimal effect on pulse rates. Relative to placebo, canagliflozin minimally influenced the changes in blood pressures observed after standing from the supine position with low incidence of asymptomatic orthostatic hypotension. No clinically meaningful changes in ECG parameters were observed with canagliflozin.

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

CONCLUSION(S): In subjects with T2DM on metformin and an ACEI or ARB:

- Canagliflozin 300 mg/day treatment reduced mean PV from baseline by approximately 5% and relative to placebo by approximately 10% at Week 1. Mean PV returned to near baseline values after 12 weeks of treatment.
- Canagliflozin treatment produced a small increase in 24-hour urine volume at Week 1 that attenuated at Week 12, and was not associated with meaningful increases relative to placebo in either 24-hour sodium or potassium excretion at either time point.
- Canagliflozin provided clinically important improvement in HbA_{1c} and FPG.
- Canagliflozin led to clinically significant BW loss over the 12-week treatment period.
- Canagliflozin lowered systolic and diastolic blood pressures, without an increase in orthostatic blood pressure changes and with a transient small increase in standing pulse rate at Week 1 that resolved after 12 weeks of treatment.
- Canagliflozin increased fractional excretion of uric acid and lowered serum uric acid levels, such that total urinary uric acid excretion at Week 12 was not meaningfully changed. Canagliflozin did not meaningfully affect urine pH.
- Canagliflozin was well-tolerated, with a safety profile consistent with the Phase 3 study results.

Disclaimer

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.