Janssen Research & Development

Clinical Study Report Synopsis dated 25 January 2011
[Protocol 28431754DIA2001; Phase 2b]

JNJ-28431754 (Canagliflozin)

Redaction and Removal of Information in This Document

- Information (including individual data listings, where applicable) has been removed or redacted to protect the privacy of patients, study subjects, and all named persons associated with the study. Names of companies other than Janssen Research & Development or Johnson & Johnson affiliates have been redacted, unless a contractual agreement is in place with those companies to disclose their names.
- Information has been removed or redacted to protect commercially confidential information.
- Aggregate data have been included, with any direct reference to an individual patient or study subject excluded.
- To disclose as much scientifically useful data as possible, no information other than that outlined above has been removed or redacted.

1. PURPOSE OF THE ERRATUM

This is an erratum to the 28431754DIA2001 Clinical Study Report (CSR) issued on 25 January 2011. The correction noted here only applies to the text of the CSR and the corresponding text in the CSR synopsis; it does not affect any of the supporting data in the CSR or the overall conclusions of the study.

2. CORRECTION IN THE CLINICAL STUDY REPORT

In the following text from Section 7.2.2.4.1. Vulvovaginal Adverse Events, the overall number of vulvovaginal adverse event recurrences, 2, is correct, however, the subject assignment to the 50 mg treatment group is incorrect. The second recurrent event occurred in the 300 mg bid treatment group (deletions are in strikeout text and additions are in bolded, italicized text):

- There were 2 vulvovaginal adverse event recurrences (defined as more than 1 vulvovaginal adverse event in the same subject with no overlap of time), including ~~1 subject in the canagliflozin 50 mg qd cohort and~~ 1 subject in the canagliflozin 200 mg qd cohort ***and 1 subject in the 300 mg bid cohort*** (Attachment 4.3.1).

The rationale for the correction is as follows:

- Subject [redacted] in the 50 mg qd group had 2 vulvovaginal adverse events (vulvovaginal mycotic infection and genital rash), which occurred on the same day (Day 87) and therefore the events did not meet the definition of recurrence. This subject was included in the text in error.
- Subject [redacted] in the 300 mg bid group had a vulvovaginal adverse event with the same preferred term (vulvovaginal mycotic infection) on Days 18 (resolved in 12 days), 32 (resolved in 17 days), and 57 (resolved in 8 days). This subject was omitted from the text in error.

All women in Study DIA2001 with treatment-emergent vulvovaginal adverse events are listed in Attachment 4.3.1 of the DIA2001 CSR.

3. CORRECTION IN THE CLINCAL STUDY REPORT SYNOPSIS

The following correction applies to the corresponding text in the CSR synopsis:

> There were 2 vulvovaginal adverse event recurrences (defined as more than 1 vulvovaginal adverse event in the same subject with no overlap of time), ~~including 1 subject in the canagliflozin 50 mg qd cohort and~~ 1 subject in the canagliflozin 200 mg qd cohort ***and 1 subject in the 300 mg bid cohort***.

4. DISCUSSION/CONCLUSION

The above correction to the text of the CSR and the corresponding CSR synopsis does not affect any of the supporting data in the CSR and does not change the overall conclusions of the study.

SYNOPSIS

Issue Date: 25 January 2011
Document No.: EDMS-PSDB-10379357:3.0

Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development
Name of Finished Product	canagliflozin
Name of Active Ingredient(s)	JNJ-28431754

Protocol No.: 28431754DIA2001 (Amendment INT-3)

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Double-Dummy, Parallel-Group, Multicenter, Dose-Ranging Study in Subjects With Type 2 Diabetes Mellitus to Evaluate the Efficacy, Safety, and Tolerability of Orally Administered SGLT2 Inhibitor JNJ-28431754 With Sitagliptin as a Reference Arm

Eudra CT Number: 2007-006693-28

Principal Investigator: [redacted] MD – [redacted]

Publication (Reference): None

Study Period: 27 March 2008 to 28 January 2009; database lock: 18 February 2009

Phase of Development: 2b

Objectives: The primary objective of this dose-ranging study was to evaluate the effects of JNJ-28431754 (canagliflozin) compared with placebo on the change in glycosylated hemoglobin (HbA1c) from baseline to Week 12 in subjects with type 2 diabetes mellitus (T2DM). Secondary objectives were to compare the effects of canagliflozin relative to placebo on: (1) the change in fasting plasma glucose (FPG) from baseline through Week 12; (2) the proportion of subjects with HbA1c <6.5% and <7.0% at Week 12; (3) the change in 7-point self-monitored blood glucose (SMBG) profiles from baseline through Week 12; (4) the proportion of subjects with symptomatic hypoglycemia and the incidence of symptomatic hypoglycemia throughout the study; (5) the proportion of subjects and the time to protocol-specified study discontinuation due to loss of glycemic control; (6) the absolute change in body weight (BW) and percentage change in BW from baseline through Week 12; (7) the change in fasting overnight urinary glucose to creatinine ratio from baseline through Week 12; (8) to assess the safety and tolerability of canagliflozin compared with placebo and; (9) to assess the pharmacokinetic (PK) exposure, explore exposure-response relationships, and develop a population PK model.

Methods: This Phase 2b study was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, dose-ranging design with 7 treatment cohorts including an active reference arm. The study assessed the safety and efficacy of canagliflozin at doses of 50 mg once daily (qd), 100 mg qd, 200 mg qd, 300 mg qd, and 300 mg twice daily (bid) versus placebo over a 12-week treatment period in subjects with T2DM who had not achieved optimal glycemic control while receiving near maximal/maximally effective doses of metformin equal to or greater than 1,500 mg/day. Subjects were stratified by whether they participated in the MMTT. The study consisted of 3 phases: (1) a 3- to 4-week pretreatment screening phase, (2) a 12-week double-blind treatment phase, and (3) a 2-week post-treatment phase. The total duration of the study was approximately 18 weeks. Three interim analyses of selected unblinded safety and efficacy data were to be performed by the [redacted] to identify active treatment groups, identify safety or tolerability issues and facilitate planning, design, and timing of the Phase 3 program.

Number of Subjects (planned and analyzed): Approximately 420 men and women that met the study entrance criteria were to be enrolled in the study to achieve a total sample of at least 378 subjects (54 subjects/treatment group) who completed the double-blind treatment phase through Week 12. A total of

451 subjects from 85 study sites in 13 countries were randomized to 1 of 7 treatment cohorts as follows: placebo, n=65; canagliflozin 50 mg qd, n=64; 100 mg qd, n=64; 200 mg qd, n=65, 300 mg qd, n=64 and 300 mg bid, n=64 subjects, and sitagliptin 100 mg qd (reference arm; sitagliptin)), n=65 subjects. Of these, 402 subjects completed the double-blind treatment phase with subjects distributed as follows: placebo, n=55; canagliflozin 50 mg qd, n=59; 100 mg qd, n=59; 200 mg qd, n=56; 300 mg qd, n=56; 300 mg bid, n=57; and sitagliptin, n=60 subjects. The intent-to-treat (ITT) analysis set included all 451 subjects randomized to treatment and the safety analysis set included all randomized subjects who received at least 1 dose of double-blind study medication and for whom safety endpoints were available. The per-protocol (PP) analysis set (ie, includes subjects who completed the study without major protocol deviations) included 396 subjects.

Diagnosis and Main Criteria for Inclusion: Men and women aged 18 to 65 years, inclusive, with a diagnosis of T2DM who had HbA1c levels ≥7% and ≤10.5% at Week -3 (screening visit), were taking a stable daily dose of metformin equal to or greater than 1,500 mg/day for at least 3 months at Week -3, had a BMI 25 to 45 kg/m^2 (except those of Asian descent who must have had a BMI 24 to 45 kg/m^2), had stable BW (ie, increased or decreased <5% within 3 months of Week -3), and with a serum creatinine concentration <1.5 mg/dL (137 μmol/L) for men and <1.4 mg/dL (128 μmol/L) for women were eligible for enrollment into the study. Subjects with prior exposure or know contraindication or suspected hypersensitivity to canagliflozin (or its excipients), sitagliptin, or metformin, or who had a history of diabetic ketoacidosis, type 1 diabetes mellitus, pancreas or beta-cell transplantation, active proliferative diabetic retinopathy, or a history of hereditary glucose-galactose malabsorption, or primary renal glucosuria were excluded from enrollment in the study.

Test Product, Dose and Mode of Administration, Batch No.: Canagliflozin was supplied as overencapsulated tablets to form capsules in the following active strengths: 50 mg (Manufacturer Lot Number PD-2778; expiration date June 2009), 100 mg (Manufacturer Lot Number PD-2779; expiration date June 2009), 200 mg (Manufacturer Lot Number PD-2780; expiration date June 2009), and 300 mg (Manufacturer Lot Numbers PD-2781, expiration date June 2009; PD-2782, expiration date June 2009; and PD-2783, expiration date July 2009). Canagliflozin was administered orally at doses of 50 mg qd, 100 mg qd, 200 mg qd, 300 mg qd, and 300 mg bid.

Reference Therapy, Dose and Mode of Administration, Batch No.: Sitagliptin was administered orally at a dose of 100 mg qd and was supplied as overencapsulated tablets at the dose strength of 100 mg (Manufacturer Lot Number PD-2777, expiration date February 2010). Placebo was administered orally bid and supplied as capsules matching canagliflozin in size and appearance by the sponsor (Manufacturer Lot Number PD-2776, expiration date 2012).

Duration of Treatment: The total planned duration of therapy was 12 weeks.

Criteria for Evaluation:

Efficacy Criteria: The primary efficacy endpoint was the change in HbA1c (%) from baseline through Week 12 (LOCF). Secondary efficacy criteria included: (1) change in HbA1c (%) from baseline to Weeks 6 and 9; (2) change in FPG from baseline to Weeks 6 and 12; (3) proportion of subjects with HbA1c <6.5% and <7.0% at Week 12; (4) change in 7-point SMBG profile from baseline to Weeks 6 and 12; (5) proportion of subjects with symptomatic hypoglycemia and the rate of symptomatic hypoglycemia through Week 12; (6) portion of subjects and the time to protocol-specified discontinuation due to loss of glycemic control; (7) absolute and % change in BW from baseline to Weeks 3, 6, 9, and 12; and (8) change in overnight urinary glucose to creatinine ratio from baseline to Weeks 3, 6, and 12.

Pharmacokinetic (PK) Evaluations: In all subjects, venous blood samples were collected predose at Weeks 3, 6, and 12 for determination of trough levels of canagliflozin and its metabolites JNJ-41488525 (M7) and JNJ-41980874 (M5), and for attainment of steady-state drug levels. More intensive sample collection for PK analysis was done at Day 1 and Week 12 in subjects undergoing the MMTT.

Pharmacodynamic (PD) Evaluations: PD evaluations included: (1) change from baseline in overnight urinary glucose and creatinine levels at Weeks 3, 6, and 12 in all subjects; (2) changes in UGE during MMTT from baseline to Week 12 based on two-hour urine collection and; (3) changes from baseline to

Week 12 in plasma glucose (AUC_{0-2h}), plasma insulin (AUC_{0-2h}), serum C-peptide (AUC_{0-2h}), plasma GLP1 (total and active; with log transformation), and plasma peptide-YY (PYY) (AUC_{0-2h}) were determined at -15, 30, 60, 90, and 120 minutes of the MMTT.

Pharmacogenomic Evaluations: An optional pharmacogenomic sample (10 mL) was collected on Day 1 to allow for pharmacogenomic research, as necessary.

Safety Evaluations: Safety was monitored throughout the study via adverse event (AE) reporting; changes in clinical laboratory tests (hematology, serum chemistry, urinalysis); ECGs (RR, PR, QRS, QT, QT corrected intervals according to Fridericia [QTcF] and Bazett [QTcB]), heart rate, T- and U-wave morphologies); physical examinations and anthropometric measurements; vital signs measurements (pulse, SBP, DBP); assessment of urinary albumin excretion and markers of renal and proximal tubular function, assessment of calcium and phosphate homeostasis, bone turnover markers and hormones regulating calcium and phosphorus homeostasis; pregnancy tests; symptomatic hypoglycemia; coagulation factors (prothrombin time [PT] and partial prothrombin time [PPT]); and vaginal and urine sample collection for fungal and bacterial culture in subjects with symptoms consistent with vulvovaginal candidiasis (VVC) and urinary tract infection (UTI).

Statistical Methods: The primary statistical objective was to establish that at least 1 of the 5 canagliflozin doses provided superior glycemic control compared to placebo as measured by the change in HbA1c (%) from baseline to Week 12. For each dose of canagliflozin, the null hypothesis to be tested was that the effect of canagliflozin on the change of HbA1c (%) from baseline to Week 12 (μ_T) was the same as that of placebo (μ_C). The alternative hypothesis was that the change of HbA1c (%) from baseline for study drug (μ_T) is superior to placebo (μ_C). Assuming a difference of 0.55% ($\mu_T - \mu_C$) and a common standard deviation of 1.0% with respect to change in HbA1c (%), it was determined using a 2-sample t-test that 54 subjects per treatment group that completed Week 12 (ie, a total of 378 subjects with a randomization ratio of 1:1:1:1:1:1:1) would be required to achieve 80% power. Assuming a dropout rate of 10%, a total of 420 subjects (ie, 60 per treatment group) were required to be enrolled into the study.

Efficacy Analyses: All subjects in the intent-to-treat (ITT) analysis set were included in the efficacy analyses. For each efficacy variable, missing post-baseline data were imputed using the last-observation-carried-forward (LOCF) method. Baseline data were not carried forward. An analysis of variance (ANCOVA) model, including treatment, stratification factor, and the baseline value as a covariate, was used to analyze the primary efficacy endpoint change in HbA1c (%) from baseline to Week 12 (LOCF). Similar analyses on the primary efficacy endpoint based on the PP analysis set were performed as a sensitivity analysis to corroborate the results from the primary analysis. The primary analysis included pair-wise comparisons between each dose level of canagliflozin and placebo using Dunnett's test. In addition, a repeated measurement analysis of HbA1c (%) was performed using a mixed-effects model to evaluate the effect of treatment over time as a sensitivity analysis, provided the model's assumptions were satisfied. This model included treatment, stratification factor, time, and treatment-by-time as fixed effects, and subject as the random effect. The change in FPG and other continuous secondary endpoints were analyzed using a similar model as that used for the primary efficacy endpoint. The proportion of subjects with symptomatic hypoglycemia and other categorical secondary endpoints were summarized by treatment group and analyzed by the Cochran-Mantel-Haenszel (CMH) test. The odds ratio and its 2-sided 95% confidence interval were calculated.

Interim Analyses: Three interim analyses of unblinded safety and efficacy data were planned to be performed by the Interim Analysis Committee: (1) when approximately 105 subjects completed 3 weeks of study drug treatment; (2) when approximately 50% of enrolled subjects completed 12 weeks of study drug treatment; and (3) when approximately 220 subjects completed 12 weeks of study drug treatment. The interim analyses were to be conducted such that no bias was introduced into the ongoing study. Only the internal independent statistician and programmer (not associated with the canagliflozin development program) were unblinded to the data and were responsible for providing the interim analyses. Individual data and interim analyses results were not to be shared with study investigators, subjects, or the sponsor's internal staff involved in the study prior to the final database lock. Summary statistics, including point and interval estimates, and a graphic evaluation of the efficacy data, were to be performed by treatment group using unblinded data.

Pharmacokinetic Analyses: Plasma concentrations of canagliflozin and glucuronide metabolites (M5 and M7) at each sampling timepoint and for all PK parameters in each treatment group were summarized.

Pharmacodynamic Analyses: PD parameters and changes from baseline were summarized.

Pharmacogenomic Analyses: Genotyping and analyses were performed in an exploratory fashion; the results are presented in a separate report. Allele and genotype frequencies for analyzed genes were to be tabulated. Selected baseline measurements and efficacy endpoints were to be explored for the association with analyzed genes. Statistical evaluation of genotyping data were to be reported separately from the Clinical Study Report.

Safety Analyses: Safety was evaluated by examining the incidence and type of treatment-emergent AEs, changes in clinical laboratory test values, physical examination results, 12-lead ECGs, vital signs measurements, the incidence of symptomatic hypoglycemia, changes in bone turnover markers, and changes in renal safety markers from the screening phase through to study completion. Values and changes from baseline over time were summarized.

RESULTS: A total of 451 subjects were randomized to 1 of 7 treatment cohorts that included placebo (N=65 subjects), canagliflozin 50 mg qd (N=64), 100 mg qd (N=64), 200 mg qd (N=65), 300 mg qd (N=64), and 300 mg bid (N=64), and sitagliptin 100 mg qd (N=65 subjects). Four hundred and two subjects (89% of subjects randomized) completed the 12-week double-blind treatment period, with a similar proportion (55 to 60 subjects) across treatment groups. Overall, 49 (11%) subjects discontinued the study. The proportion was generally similar across treatment groups, with the highest proportion in the placebo and 200 mg qd groups (15% and 14%, respectively). The most common reasons for early withdrawal were withdrawal of consent (16 subjects; 4%), adverse events (11 subjects; 2%), and lost to follow-up (9 subjects, 2%). The number of subjects who withdrew due to AEs was similar across canagliflozin and placebo groups. One subject in the canagliflozin 50 mg qd group withdrew due to lack of efficacy.

Overall, demographic and baseline characteristics for the ITT analysis set were generally balanced across treatment groups, and were consistent with the T2DM population described in the study inclusion/exclusion criteria. The median age of subjects was 54 years (range 29 to 65 years), with 48% women and 52% men, and 73% of subjects were white and 25% were Hispanic or Latino. The mean (SD) baseline HbA1c (%) for all randomized subjects was 7.7 (0.93) %, mean (SD) FPG was 9.0 (2.25) mmol/L, and the mean (SD) BW and BMI were 87.1 (17.37) kg and 31.5 (4.91) kg/m^2 (classified as obese), respectively. Overall, 16% of subjects participated in the MMTT.

The majority of subjects (87%) in the ITT analysis set were in the duration of exposure window of 71 to 91 consecutive days of double-blind study medication. Nine (2%) subjects received >91 days of double-blind study medication. Overall, the mean (SD) total duration of exposure to double-blind study medication was 78.3 (19.3) days (ie, 84 days of dosing planned).

EFFICACY RESULTS: Canagliflozin produced clinically meaningful changes in the primary efficacy variable, with significant mean reductions in HbA1c (%) from baseline at Week 12 LOCF for all dose levels compared to placebo (least-squares mean differences of change in HbA1c (%) from baseline at Week 12 LOCF compared to placebo were -0.45%, -0.51%, -0.54%, -0.71%, and -0.73% for canagliflozin 50 mg qd, 100 mg qd, 200 mg qd, 300 mg qd, and 300 mg bid, respectively and -0.56% for sitagliptin). All doses of canagliflozin were statistically significant (adjusted $p<0.001$ for all comparisons) from placebo. HbA1c reductions seen in the 100 mg qd and 200 mg qd canagliflozin groups were similar and appeared to be slightly greater relative to the 50 mg qd canagliflozin group; a trend for greater HbA1c reductions was seen in the 300 mg qd and 300 mg bid canagliflozin groups relative to the 100 mg qd and 200 mg qd canagliflozin groups. The least-squares mean differences in the change of HbA1c (%) from baseline at Week 12 LOCF compared to placebo in the PP analysis set were similar in magnitude and consistent with the results obtained based on the ITT analysis set.

Results from the analysis of the secondary efficacy endpoints were consistent with changes in the primary endpoint. Fasting plasma glucose increased slightly in the placebo group and decreased in a statistically significant fashion (at $p<0.05$) relative to placebo in all canagliflozin groups and in the sitagliptin group (least-squares mean differences in change in FPG (mmol/L) from baseline at week 12 LOCF compared to

placebo were -0.9, -1.4, -1.8, -1.8, and -1.7 mmol/L for canagliflozin at 50 mg qd, 100 mg qd, 200 mg qd, 300 mg qd, and 300 mg bid, respectively). Consistent with the observed changes in FPG and HbA1c, all doses of canagliflozin produced greater reductions in mean 7-point SMBG from baseline to Weeks 6 and 12 compared to placebo. Overall, the incidence of subjects with treatment-emergent symptomatic hypoglycemia events was low, with a total of 11 (2%) subjects that reported at least 1 treatment-emergent symptomatic hypoglycemic event. Symptomatic hypoglycemic events were reported in 0% to 6% of subjects in the canagliflozin groups compared to 2% of subjects in the placebo group, and 5% of subjects in the sitagliptin group. There was no evidence of dose-dependency across canagliflozin groups and there were no severe or serious hypoglycemic reactions reported.

Percent body weight was reduced in a statistically significant fashion (at $p<0.05$) in all canagliflozin groups relative to placebo, with an apparently greater weight loss in the 300 mg qd and 300 mg bid canagliflozin groups than at lower canagliflozin doses (least-squares mean differences in % change of BW from baseline at Week 12 LOCF compared to placebo were -1.3%, -1.5%, -1.6%, -2.3%, and -2.3% for canagliflozin at 50 mg qd, 100 mg qd, 200 mg qd, 300 mg qd, and 300 mg bid, respectively and 0.4% for sitagliptin). Progressive, dose-related reductions in mean body weight over time were observed with all doses of canagliflozin and weight loss was maintained over the 12-week course of treatment, compared to no weight reduction over time in the sitagliptin group.

Overnight urinary glucose/creatinine ratio increases and overnight $RT_{glucose}$ decreases were seen in all canagliflozin groups, with maximal effects seen at 200 mg qd and higher canagliflozin dose groups (least-squares mean differences in the change of urinary glucose/creatinine ratio (mg/mg) from baseline at Week 12 LOCF compared to placebo were 36.1, 49.3, 48.2, 49.0, and 60.3 for canagliflozin at 50 mg qd, 100 mg qd, 200 mg qd, 300 mg qd, and 300 mg bid, respectively and -3.3 for sitagliptin). All doses of canagliflozin were statistically significant (adjusted $p<0.05$ for all comparisons) compared to placebo. Changes in these parameters were maximal at the first post-randomization time point and were maintained throughout the study. Canagliflozin lowered the overnight $RT_{glucose}$ across all canagliflozin groups compared to placebo and sitagliptin, with the maximal effect of canagliflozin observed at the first post-randomization visit (Week 3) and maintained through Week 12. The mean (SD) overnight $RT_{glucose}$ values at Week 12 in canagliflozin groups were: 120.20 (34.42) mg/dL at 50 mg qd; 100.09 (30.25) mg/dL at 100 mg qd; 88.40 (29.81) mg/dL at 200 mg qd; 80.31 (27.07) mg/dL at 300 mg qd, and 77.14 (23.12) mg/dL at 300 mg bid, compared to 174.73 (39.67) mg/dL for placebo and 167.59 (46.79) mg/dL for sitagliptin. The lowering of $RT_{glucose}$ by canagliflozin appeared to increase in a dose-dependent fashion from 50 mg qd to 300 mg qd and the overnight $RT_{glucose}$ was maximally lowered by canagliflozin treatment to approximately 75 mg/dL.

Generally, canagliflozin had minimal effects on lipid parameters, however, a modest trend for reductions in fasting triglycerides and total cholesterol/HDL ratio and an increase in HDL-cholesterol were seen at the 300 mg qd and 300 mg bid canagliflozin groups relative to placebo. Increases in LDL-cholesterol were observed at Weeks 6 and 12 in the canagliflozin 300 mg bid group compared to placebo (ie, least-squares mean difference of 0.226 mmol/L (p=0.06) and 0.204 mmol/L (p=0.116), respectively). A slight reduction in serum triglycerides from baseline was observed at Week 12 in the canagliflozin 300 mg qd and 300 bid groups compared to placebo (least-squares mean difference from baseline compared to placebo of -0.322 mmol/L [p=0.025] and -0.398 mmol/L [p=0.005]). An increase in HDL at Week 12 (least-squares mean difference from baseline compared to placebo of 0.050 mmol/L [p=0.115] and 0.103 [p=0.001]) and reductions in the total cholesterol/HDL ratio (least-squares mean difference from baseline compared to placebo of -0.21 [p=0.159] and -0.19 [p=0.200]) were trends observed in the canagliflozin 300 mg qd and 300 bid treatment groups respectively, but not in the sitagliptin group.

A modest trend for a reduction in sitting systolic blood pressure relative to placebo was seen in the 300 mg qd and 300 mg bid canagliflozin groups. Based on the ANCOVA model with treatment and MMTT stratum as cofactors and the corresponding baseline SBP as covariate, the least-squares mean differences compared to placebo in mean change of SBP from baseline at Week 12 LOCF were 0.97, 2.19, 0.13, -2.46, and -1.04 mmHg for canagliflozin 50 mg qd, 100 mg qd, 200 mg qd, 300 mg qd, and 300 mg bid, respectively and 1.72 mmHg for sitagliptin. None of these changes in sitting SBP were statistically significantly different relative to placebo. Diastolic blood pressure was not significantly affected by canagliflozin treatment (least-squares mean differences compared to placebo in mean change of DBP from

baseline at Week 12 LOCF were 0.62, 0.56, -0.43, -0.10, and -0.70 mmHg for canagliflozin at 50 mg qd, 100 mg qd, 200 mg qd, 300 mg qd, and 300 mg bid, respectively) and 1.26 mmHg for sitagliptin.

PHARMACOKINETIC RESULTS: Mean trough plasma concentrations of canagliflozin and its metabolites (M7 and M5) increased with increasing daily doses from 50 mg qd to 300 mg bid. At each canagliflozin dose level, the mean trough plasma canagliflozin and its metabolite concentrations were similar over the 12-week study period. Similarly, the mean plasma canagliflozin concentrations increased with increasing dose during Week 12 in the small subset of subjects who received an MMTT. There was a high degree of inter-subject variability for both the trough and post-dose/MMTT samples across the dose levels (%CV ranged from 25% to 149%).

PHARMACODYNAMIC RESULTS: Due to the small sample size and variability of these data, interpretation of pharmacodynamic data was not deemed reliable and these results were not presented in the body of the report.

PHARMACOGENOMIC RESULTS: Blood samples from 361 subjects were subjected to DNA extraction. DNA samples from 2 subjects were destroyed to conform to subject's consent. Aliquots of DNA samples from 359 subjects were analyzed. The genotype data were evaluated in an exploratory manner only, and the results were reported separately from this CSR. The DNA sample from 1 subject ([redacted]) was destroyed upon request of the subject after the Pharmacogenomic Data Report had been submitted.

SAFETY RESULTS: A total of 199 (44%) subjects overall experienced at least 1 treatment-emergent adverse events (TEAEs). The overall incidence of TEAEs ranged from 40% to 56% of subjects across canagliflozin groups, with no apparent dose response trend, compared to placebo (40%) and sitagliptin (35%). Among these most common TEAEs, vomiting (5%) and upper abdominal pain (6%) were more frequently reported in the canagliflozin 300 mg bid group, relative to other treatment groups, including placebo and sitagliptin. The incidence of vulvovaginal adverse events was higher in all canagliflozin groups without an apparent dose-dependency compared to placebo and to sitagliptin. The majority of TEAEs were considered by the investigator to be mild to moderate in severity and to be probably related or very likely related to study medication. None of the TEAEs classified by the investigator as probably related or very likely related to study drug were classified as severe. No subjects had dose reductions due to TEAEs and a small number of subjects had temporary interruption of study drug administration due to a TEAE. No deaths occurred and 6 (1%) subjects overall experienced a treatment-emergent SAE that included 1 subject in each canagliflozin group, 1 subject in the placebo group and no subjects in sitagliptin group. Infections and infestations were the most common class of SAEs, reported in 3(1%) subjects overall. No venous thromboembolic adverse events or major adverse cardiovascular events were reported. The incidence of reported hypoglycemic events in canagliflozin groups was low (0% to 6% of subjects) without evidence for dose-dependency and was similar to placebo (2% of subjects) and sitagliptin (5% of subjects). There were no severe or serious hypoglycemic events reported.

There was a low incidence of AEs leading to discontinuation, occurring in a total of 11 (2%) subjects overall. Overall the incidence of AES leading to discontinuation was similar across canagliflozin groups and placebo. No subjects in the sitagliptin group experienced a TEAE leading to discontinuation. The only specific adverse event leading to discontinuation in more than 2 (<1%) subjects overall was diarrhea, leading to discontinuation in 1 subject in the canagliflozin 300 mg qd group and 1 subject in the canagliflozin 300 mg bid group.

Overall, at least 1 treatment-emergent vulvovaginal AE was reported in a total of 31 (14%) of women subjects. The overall incidence of vulvovaginal AEs was higher in the canagliflozin groups with no apparent dose trend, compared to the placebo and sitagliptin groups. The most common vulvovaginal AEs were of the infections and infestations SOC (26 subjects, 12%) and the most common individual AE was vulvovaginal mycotic infection (15 subjects, 7%) followed by vulvovaginal candidiasis (6 subjects, 3%). There were 2 vulvovaginal adverse event recurrences (defined as more than 1 vulvovaginal adverse event in the same subject with no overlap of time), including 1 subject in the canagliflozin 50 mg qd cohort and 1 subject in the canagliflozin 200 mg qd cohort. The majority of vulvovaginal adverse events were treated with topical or systemic antifungal therapy and resolved while continuing canagliflozin. No subjects

discontinued the study due to either vaginal infection or vulvovaginal mycotic infection and none of the treatment-emergent vulvovaginal-related AEs were classified by the investigator as serious.

At baseline and endpoint, bacterial and fungal urine cultures were performed. No clinically relevant increase in positive urine cultures at endpoint was seen in canagliflozin groups relative to placebo. At baseline 10.7% of women had positive vaginal fungal cultures with *C. glabrata* being more commonly cultured than *C. albicans*. Relative to placebo an increase in positive vaginal fungal cultures was observed in all canagliflozin groups without apparent dose-dependency. Conversion from a negative vaginal fungal culture at baseline to a positive culture at endpoint occurred in placebo and canagliflozin groups but at a higher frequency in the canagliflozin groups. Logistic regression analysis identified canagliflozin treatment as a risk factor for converting from a negative vaginal fungal culture at baseline to a positive culture at endpoint.

While changes in certain laboratory measurements were noted in canagliflozin groups, routine laboratory monitoring did not reveal a canagliflozin-associated safety signal. Changes noted in canagliflozin groups relative to placebo included: (1) modest increases in serum magnesium (range of mean increase: 0.044 to 0.082 mmol/L at Week 12 in canagliflozin groups compared to placebo: mean decrease of -0.003 mmol/L at Week 12); (2) BUN (range of mean increase: 0.31 to 0.74 mmol/L at Week 12 in canagliflozin groups compared to placebo: mean increase of 0.10 mmol at Week 12); (3) hematocrit (range of mean increase: 0.011 to 0.026 at Week 12 in canagliflozin groups compared to placebo: -0.00 at Week 12); (4) hemoglobin (range of mean increase: 3.2 to 8.1 g/L at Week 12 in canagliflozin groups compared to placebo: 0.7 g/L at Week 12); (5) transient increases in serum creatinine (range of mean increase: 3.8 to 5.6 μmol/L) from baseline at Week 3 in all canagliflozin groups compared to placebo: 1.9 μmol/L) and PTH that returned to normal while on treatment; (6) decreases in serum urate (range of mean decrease: -31.5 to -57.0 μmol/L at Week 12 in canagliflozin groups compared to placebo: mean decrease of -3.4 μmol/L at Week 12); and (7) modest increases in serum CTX and in urinary NAG/creatinine ratio that tended to diminish with continued treatment.

Of the bone turnover markers and hormones regulating calcium and phosphorous homeostasis measured during the study, only collagen type-1 beta-carboxy telopeptide (CTX), a marker of bone resorption, was affected by canagliflozin treatment, increasing progressively over the 12 weeks of treatment relative to placebo in an apparent dose-dependent fashion from 50 mg qd to 200 mg qd, without further increases at higher canagliflozin doses.

The urine albumin/creatinine ratio was slightly decreased in all canagliflozin groups (range of mean change of -4.8 to -25.4 mg/g at Week 12) relative to placebo (mean change of 0.0 mg/g at Week 12). Consistent with the changes in serum creatinine, eGFR decreased in all canagliflozin groups at Week 3 (range of mean decrease of -5.74 to -8.20 ml/min/1.73m^2) relative to placebo (mean change of -3.45 ml/min/1.73m^2) and returned to baseline values by Week 12.

No clinically relevant safety signals were detected in vital sign measurements, ECG parameters, or physical examination findings in canagliflozin groups relative to placebo.

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

CONCLUSIONS:

- In all canagliflozin groups there were statistically significant HbA1c reductions relative to placebo in a population of subjects with type-2 diabetes not optimally controlled on maximal/near maximal metformin therapy.
- HbA1c reductions seen in the 100 mg qd and 200 mg qd canagliflozin groups were similar and appeared to be slightly greater relative to the 50 mg qd canagliflozin group; a trend for greater HbA1c reductions was seen in the 300 mg qd and 300 mg bid canagliflozin groups relative to the 100 mg qd and 200 mg qd canagliflozin groups.

- There was greater reduction from baseline in fasting plasma glucose for all canagliflozin groups compared to placebo. The effects of canagliflozin on fasting plasma glucose were maximal at the earliest post randomization time point and were sustained at Week 12. Maximal decreases in fasting plasma glucose were seen in the 200 mg qd and greater canagliflozin dose groups.
- There was greater reduction from baseline in % body weight for all canagliflozin groups compared to placebo. In canagliflozin groups weight loss continued throughout the study. Maximal decreases in % body weight were seen in the 300 mg qd and 300 mg bid canagliflozin dose groups. Similar directional changes in canagliflozin groups were generally noted in absolute changes in body weight, BMI and anthropometric assessments.
- There was a greater increase from baseline in overnight urinary glucose to creatinine ratio (mg/mg) and decreases in overnight $RT_{glucose}$ for all canagliflozin groups compared to placebo. Maximal increases in urinary glucose to creatinine ratio and decreases in overnight $RT_{glucose}$ were seen in 200 mg qd and greater canagliflozin dose groups. Canagliflozin effects on these parameters were maximal at the earliest post-randomization time point and were sustained through Week 12. In canagliflozin groups, the maximal lowering of the overnight $RT_{glucose}$ was to 75 mg/dL which suggests a low likelihood of hypoglycemic events when canagliflozin is used as monotherapy or in combination with other antihyperglycemic agents not associated with hypoglycemia.
- The incidence of reported hypoglycemic events in canagliflozin groups was low without evidence for dose-dependency and was similar to placebo and sitagliptin groups. There were no severe or serious hypoglycemic events reported.
- The possible trend for improvements in triglyceride, HDL and total cholesterol/HDL and reductions in systolic blood pressure at canagliflozin doses of 300 mg qd and greater coupled with improved glycemic control and weight loss could lead to a reduction in cardiovascular events.
- Canagliflozin administered orally at doses up to 300 mg bid for 12 Weeks is safe and generally well tolerated.
- Positive vaginal fungal cultures with *C. glabrata* and to a lesser extent *C. albicans* were seen at baseline in a significant proportion of asymptomatic women and conversion from a negative vaginal fungal culture at baseline to a positive culture at endpoint was also seen in a significant proportion of women treated with placebo not reporting vulvovaginal adverse events. Thus, asymptomatic vaginal colonization with Candida spp commonly occurs in women with type-2 diabetes.
- At all doses tested and without evidence for dose-dependency, canagliflozin was associated with increases in symptomatic genital and vulvovaginal adverse events. These adverse events were generally mild, did not lead to discontinuation and responded to standard antifungal therapy. Vaginal colonization with Candida spp prior to treatment and residence in Canada/US were apparent risk factors for vulvovaginal adverse events. Conversion from negative vaginal fungal culture at baseline to positive vaginal fungal culture at endpoint occurred in placebo and all canagliflozin groups with the frequency of conversion being higher in canagliflozin groups.
- No clinically meaningful increases in canagliflozin groups were seen in the reporting of preselected adverse events of interest (urinary tract infections, hypovolemia-related, skin, fracture, and renal adverse events).
- In canagliflozin groups there was a modest, transient increase in serum creatinine and a reduction in eGFR. Small sustained increases in BUN were seen in canagliflozin groups possibly due to a mild intravascular volume contraction secondary to an osmotic diuresis.
- Except for a transient increase in urinary NAG excretion possibly secondary to glucosuria, canagliflozin did not adversely affect proximal tubule function.
- While markers of bone formation and two markers of bone resorption were unaffected by canagliflozin treatment, a modest increase in serum CTX, another marker of bone resorption, was observed in canagliflozin groups. No other clinically meaningful changes in calcium/phosphorous homeostasis or in the hormones regulating calcium homeostasis were noted in canagliflozin groups. The clinical relevance of the isolated serum CTX finding is not certain.

- In summary, no dose-limiting safety or tolerability findings were noted at doses up to 300 mg bid and there are no new, unusual, or unexpected, clinically significant safety signals that would prevent canagliflozin from being studied further in Phase 3 trials.