SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Investigational Product	JNJ-28431754 ((canagliflozin))

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Status: Approved

Date: 29 June 2016

Prepared by: Janssen Research & Development, LLC

Protocol No.: 28431754DIA1055

Title of Study: Open-Label, Multicenter, Multiple Oral Dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Canagliflozin in Older Children and Adolescents ≥10 to <18 years of age with Type 2 Diabetes Mellitus and Currently on a Stable Dose of Metformin

NCT No.: NCT02000700

Clinical Registry No.: CR103045

Coordinating Principal Investigator: William Tamborlane, MD; Yale University School of Medicine, [redacted] USA

Study Centers: 19 centers in 2 countries

Publication (Reference): None

Study Period: 06 April 2014 to 01 April 2016

Phase of Development: 1

Objectives: The primary objective of this study was to evaluate the pharmacokinetics of canagliflozin after multiple oral doses of canagliflozin in children and adolescent subjects with Type 2 Diabetes Mellitus (T2DM) who were ≥10 to <18 years of age and on a stable dose of metformin.

The secondary objectives were to:

- evaluate the pharmacodynamic effects of canagliflozin on plasma glucose levels, urinary glucose excretion, and the renal threshold for glucose after multiple oral doses and
- assess the acceptability of the canagliflozin tablets
- assess the safety and tolerability

Methodology: This was an open-label, sequential, multiple-dose (14 days of dosing), multi-center study of canagliflozin in 2 dose groups of approximately 8 subjects per dose group (up to approximately 16 children and adolescents in total). Subjects who were diagnosed with T2DM and on a stable regimen of metformin (at a dose of at least 1,000 mg per day) for at least 8 weeks before screening were enrolled in the study. Subjects were instructed to continue to take their stable dose of metformin throughout the study.

The study consisted of 4 phases:

- a Screening Phase of approximately 3 weeks (Days -25 to -4)
- a Baseline Phase of 3 days (Days -3 to -1)
- an Open-Label Treatment Phase of a 17-day Treatment Period (Days 1 through 17) and
- a safety Follow-up Phase which occurred 7 to 10 days after the last study-related procedure on Day 17 or at the time of early withdrawal

At the screening visit the subjects were evaluated for inclusion and exclusion criteria. Subjects were to fast overnight for a minimum of 8 hours before collection of any screening clinical laboratory evaluations.

Subjects who met all inclusion and none of the exclusion criteria were admitted to the study center in the evening of Day -2 or in the morning of Day -1 for collection of safety and pharmacodynamic assessments. Subjects received a placebo dose with approximately 180 mL water on Day -1 after an overnight fast of at least 8 hours. Approximately 10 minutes after placebo dosing, subjects received a standardized breakfast. Serial blood samples were obtained immediately before dosing and at selected time points for up to 24 hours.

After completion of the Baseline Phase, eligible subjects continued into the Treatment Phase and were enrolled into each dose group in sequential order as follows:

- Dose Group 1: Eight subjects received 100 mg (as 1×100-mg tablet) of canagliflozin daily for 14 days.
- Dose Group 2: Based upon an acceptable review of pharmacokinetic, pharmacodynamic and safety data from the first 5 subjects who completed the study in Dose Group 1, 9 additional subjects were enrolled into Dose Group 2 to receive 300 mg (as 1×300-mg tablet) of canagliflozin daily for 14 days. An interim analysis of the available safety, PK and PD data from the first 5 subjects receiving 100 mg of canagliflozin was completed on 02 March 2015. Since the interim safety, PK and PD parameters were comparable to those observed in adults with T2DM receiving 100 mg of canagliflozin, the 300 mg dose was selected for Group 2.

In both dose groups, all subjects received their first dose of study drug in the morning of Day 1 after an overnight fast of at least 8 hours. Approximately 10 minutes after dosing, subjects received a standardized breakfast. Subjects remained at the study center for approximately 4 hours and were discharged if there were no safety-related issues. Subjects were given instructions to continue daily oral doses of canagliflozin with metformin for an additional 12 consecutive days (Day 2 to Day 13) at approximately the same time each morning before the first meal of the day under the supervision of a primary care giver (eg, parent or legally accepted representative). The clinical study center contacted the subjects each day to remind them to take their dose of study medication as well as metformin, to query potential adverse events and to ensure compliance with study-related procedures.

Subjects or their primary care giver were to record the time and amount of each dose as well as their daily fasting self-glucose monitoring value in their study diary. Subjects and their caregivers were given instructions to return to the study center in the evening of Day 13 or in the morning of Day 14 after an overnight fast of at least 8 hours.

Subjects received their final dose of study drug in the morning of Day 14. A questionnaire to assess the acceptability of the canagliflozin tablet was administered immediately following this. Approximately 10 minutes after dosing, subjects received a standardized breakfast and remained at the study center for collection of pharmacokinetic, pharmacodynamic and safety assessments for 24 hours (until the morning of Day 15). After collection of all pharmacokinetic, pharmacodynamic and safety assessments on Day 15, subjects were discharged from the study center and were given instructions to undergo pharmacokinetic and safety assessments in the mornings on Day 16 and Day 17, which occurred either at their home (by

the study nurse) or in the study center, depending on the feasibility assessment. Subjects were instructed to return to the study center in 7 to 10 days for a final safety follow-up assessment. For subjects who withdrew early, the final safety assessment occurred as soon as possible after last study drug administration.

During the last 3 days of Screening (ie., Days -6, -5, and -4) and on a daily basis during the entire treatment outpatient period (Day 2 to Day 13 and Day 15 to follow-up), subjects or their primary care giver were to record the subject's fasting self-monitored fingerstick glucose levels (before the first meal of the day) in a diary which was provided to them, and report the results to the clinic weekly, or at any time where values exceeded pre-specified limits (>270 mg/dL or <50 mg/dL). This information was collected by the clinical study center and recorded in the electronic case report form (eCRF). On Day -1, Day 1 and again on Day 14 and Day 15, the study staff monitored the subject's fasting glucose levels via a fingerstick blood sample.

Number of Subjects (planned and analyzed):

Planned: A total of 16 subjects were planned to be enrolled in the study.

Analyzed: A total of 17 subjects (8 subjects from Group 1 receiving 100 mg and 9 subjects from Group 2 receiving 300 mg canagliflozin) completed the study and included in the analysis.

Diagnosis and Main Criteria for Inclusion: Medically stable male or female subjects ranging in age from ≥10 to <18 years, with diagnosis of T2DM without pancreatic autoimmunity and who were on a stable regimen of metformin immediate release (IR) monotherapy of at least 1,000 mg/day for at least 8 weeks before screening were enrolled in the study. Subjects had to be able to swallow whole tablets and had to have normal renal function (estimated glomerular filtration rate [eGFR] ≥90 ml/min/1.73 m^2 as assessed by Schwartz formula), ALT or AST <2.0×ULN and a hemoglobin A_{1c} (HbA_{1c}) of ≥6.1% to ≤10%.

Subjects with history of type 1 diabetes mellitus (T1DM), history of maturity onset diabetes of the young and any secondary form of diabetes were excluded.

Test Product, Dose and Mode of Administration, Batch No.:

Canagliflozin, tablet, 100 mg (1×100-mg tablet), oral

Canagliflozin, tablet, 300 mg (1×300-mg tablet), oral

Placebo, tablet, oral

The batch numbers and expiration dates were as follows:

Reference Number	Description	Expiry Date
4368017	Canagliflozin 100mg	Apr-16
4368018	Canagliflozin 300mg	Feb-16
4368077	Placebo for Canagliflozin 100mg	Sep-16
4369036	Placebo for Canagliflozin 100mg	Sep-16
4369038	100mg Canagliflozin 25ct Bottle	Apr-16
4369039	Canagliflozin 300mg	Feb-16
4371868	Placebo for Canagliflozin 100mg	Sep-16
4372063	300mg Canagliflozin 25ct Bottle	Apr-17

Duration of Treatment: The duration of treatment was 14 days. The total duration of study for an enrolled subject including the screening period and follow up was 51 days.

Criteria for Evaluation:

Pharmacokinetics

Venous blood samples (2 mL each) were collected at predetermined timepoints for up to 72 hours after dosing on Day 14 for determination of plasma canagliflozin concentrations.

Based on the individual concentration-time data, given actual sampling times, the following plasma pharmacokinetic parameters of canagliflozin were determined for each dose as appropriate: Day 14; $C_{max,ss}$, t_{max}, AUC_{τ}, λz, $t_{1/2,\lambda}$, λ_z, and CL_{ss}/F.

The determination of canagliflozin and or metabolite (M5 and M7) concentrations in urine and plasma (metabolites only) were not performed at this time.

Pharmacodynamics

Blood samples (1.2 mL each) were collected for the measurement of plasma glucose at predetermined timepoints throughout the 24-hour interval on Day -1 of the Baseline Phase and after dosing on Day 14 of the Treatment Phase.

All urine was collected for measurement of urine glucose concentrations throughout 24 hours (0- to 12-hour and 12- to 24- hour intervals) from all subjects on Day -1 of the Baseline Phase and again on Day 14 of the Treatment Phase after dosing.

The following pharmacodynamic parameters were determined: fasting plasma glucose (FPG), mean plasma glucose (MPG: $MPG_{0-4h,}$ MPG_{0-24h}), mean incremental (above pre-meal) plasma glucose (MΔPG, $M\Delta PG_{0-2h}$, and $M\Delta PG_{0-4h}$), urinary glucose excretion (UGE: UGE_{0-12h}, UGE_{12-24h} and UGE_{0-24h}) and renal threshold for glucose excretion (RT_G; RT_{G0-12h}, $RT_{G12-24h}$, and 24-h mean RT_G).

Pharmacogenomics

Two buccal swab samples were collected on Day 1 from all enrolled subjects to allow pharmacogenomics analysis. DNA samples were to be analyzed for the *UGT1A9* and *UGT2B4* genes. Subject participation in the pharmacogenomic research was required.

Safety

Safety evaluations included collection of adverse events (including events of hyperglycemia and hypoglycemia), assessment of fasting fingerstick glucose values, vital signs (blood pressure and pulse rate), physical examinations (including body temperature), 12-lead electrocardiograms (ECGs), and fasting safety laboratory tests including hematology, clinical chemistry, and urinalysis. Fasting plasma glucose (FPG) was obtained at Screening and on Days -1 and 14.

The total amount of blood to be drawn for clinical laboratory tests, pharmacokinetic and pharmacodynamic evaluations was approximately 114 mL.

Acceptability of the Tablet

The study allowed an assessment of the acceptability (eg, taste, smell, swallowability) of the canagliflozin tablets by the subjects. On Day 14, immediately after study drug administration, and before breakfast, subjects were asked to complete a questionnaire in order to assess the acceptability of the canagliflozin tablet they received. Results were summarized descriptively.

Statistical Methods:

Sample Size Determination

The intrasubject coefficient of variation (CV) for AUCs and C_{max} after multiple dose administration of canagliflozin is estimated to be less than 25% based on previous studies in adult subjects. Assuming an estimated CV of 25% for AUC and C_{max} in the pediatric population, a sample size of 8 completed subjects per dose group was considered to be sufficient to estimate the mean AUC and C_{max} for that group to be within 81% and 123% of their true values with 95% confidence. A sample size of 5 completed subjects (for interim review of pharmacokinetic, pharmacodynamic and safety data) per dose group was considered to be sufficient to estimate the mean AUC and C_{max} for that group to be within 73% and 136% of their true values with 95% confidence.

Based on previous studies in healthy adult subjects, the CVs for the 24-h mean RT_G, UGE_{24h}, mean plasma glucose MPG_{0-2h}, MPG_{0-4h} and MPG_{0-24h} was assumed to be less than or equal to 33%. Thus, using an estimated CV of 33% for the pharmacodynamic parameters, a sample size of 8 completed subjects per group would be sufficient for estimated mean pharmacodynamic parameters for that group to fall within 76% and 132% of the true value with 95% confidence. A sample size of 5 completed subjects (for an interim review of pharmacokinetic, pharmacodynamic and safety data) per dose group would be sufficient for estimated mean pharmacodynamic parameters for that group to fall within 66% and 151% of the true value with 95% confidence.

Pharmacokinetics

Individual and mean canagliflozin plasma concentration-time profiles were plotted for each canagliflozin dose after multiple dosing. Plasma concentration data at each time point was summarized with mean, median, geometric mean, minimum, maximum, standard deviation (SD) and coefficient of variation (%) for each dose. All plasma pharmacokinetic parameters of canagliflozin were summarized per dose with mean, median, geometric mean, minimum value, maximum value, SD, and coefficient of variation (%).

Pharmacodynamics

FPG, RT_{G0-12h}, $RT_{G12-24h}$, 24-h mean $RT_{G,}$ UGE_{0-12h}, UGE_{12-24h}, UGE_{0-24h}, MPG_{0-4h}, MPG_{0-24h}, $M\Delta PG_{0-2h}$ and $M\Delta PG_{0-4h}$ from Day -1 and Day 14 were summarized with descriptive statistics for each treatment.

Pharmacogenomics

Allele and genotype frequencies for analyzed genes were tabulated. Selected pharmacokinetic parameters of canagliflozin after multiple oral doses of canagliflozin were explored for association with variation in the *UGT1A9* and *UGT2B4* genes.

Acceptability of the Tablet

On Day 14, immediately after study drug administration, and before breakfast, subjects were administered a questionnaire in order to assess the acceptability of the canagliflozin tablet. Results were summarized descriptively.

Safety

All subjects who received at least 1 dose of canagliflozin were included in the safety and tolerability analysis. Baseline for post dose vital sign assessments was defined as the time matched Day -1 predose evaluation. Baseline measurements for clinical laboratory tests were the measurements arising from the last laboratory evaluation before the study drug administration. Baseline for ECG was defined as the Screening evaluation. Safety was evaluated by examining the incidence and type of adverse events, change from baseline in vital signs measurements, physical examination, 12-lead ECGs, and safety clinical laboratory tests including self-monitored fingerstick glucose. For urine electrolytes (calcium,

phosphate, and creatinine) and albumin, cumulative amount over a 24 hour period was reported on Day -1 and Day 14.

RESULTS:

STUDY POPULATION:

A total of 17 subjects were enrolled (8 subjects from Group 1 [100 mg] and 9 subjects from Group 2 [300 mg]) and received the study medication. All 17 subjects enrolled completed the study.

The demographic and baseline characteristics were similar between both the groups. The majority of the subjects were black or African American. There were more female subjects than male subjects (12 subjects vs 5 subjects). The subjects had a median age of 15 years (range: 11 to 17 years, 47% between ages 10 to 14 years, 53% between ages 15 to 18 years). The 3-fold range of body mass index (BMI) and body weight included within this study were notable, with a mean BMI value of 38.17 kg/m^2 (range: 18.0 to 55.3), and a mean weight value of 107.15 kg (range: 48.5 to 168.6). The mean baseline HbA_{1c} was 6.91%, mean baseline FPG was 6.62 mmol/L and mean baseline eGFR was 149.3 ml/min/1.73 m^2.

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:

Pharmacokinetic

Seventeen pediatric subjects (8 subjects from Group 1 [100 mg] and 9 subjects from Group 2 [300 mg]) are included in the pharmacokinetic analysis. One sampling time point was excluded from analysis of the canagliflozin plasma concentration data due to the sampling time deviating by more than 20% from the scheduled time. Otherwise, no other exclusions were made to the plasma concentration data.

The mean plasma canagliflozin concentration time profiles from this analysis were higher for the 300 mg dose (Group 2) vs. the 100 mg dose (Group 1).

Plasma canagliflozin concentrations increased rapidly following administration of both treatments. Mean t_{max} for canagliflozin after 14 days of once daily 100- or 300-mg dose administration ranged from 1.64 to 2.44 hours (range of 1 to 4 hours) across both treatments. Mean C_{max} and AUC_{τ} values in the 9 pediatric T2DM subjects receiving canagliflozin 300 mg once daily were higher than the 8 pediatric T2DM subjects receiving canagliflozin 100 mg once daily. Mean $t_{1/2}$ for canagliflozin after 14 days of once daily 100- or 300-mg dose administration ranged from 11.3 to 15.2 hours (range of 8.0 to 29.3 hours) across both treatments.

In general, the pharmacokinetics observed in the 8 pediatric T2DM subjects receiving 100 mg once daily and the 9 pediatric T2DM subjects receiving 300 mg once daily doses of canagliflozin were consistent with those of adult subjects.

Mean (SD) Plasma Canagliflozin Pharmacokinetic Parameters

(Study 28431754DIA1055: Pharmacokinetic Analysis Set)

Parameters	Canagliflozin 100 mg (Group 1) n= 8	Canagliflozin 300 mg (Group 2) n= 9
C_{max} (ng/mL)	951 (429)	3,260 (1,330)
C_{max}/Dose (ng/mL/mg)	9.51 (4.29)	10.9 (4.42)
t_{max} (h)[a]	1.64 (1.00 – 1.98)	2.44 (1.00 - 4.00)
AUC_{τ} (h*ng/mL)	6,190 (1,770)	28,392 (12,412)
AUC_{τ}/Dose (h*ng/mL/mg)	61.9 (17.7)	94.6 (41.4)
$t_{1/2}$ (h)	11.3 (2.5)	15.2 (6.9)
λ_z (1/h)	0.0644 (0.0151)	0.0528 (0.0183)
CL_{ss}/F (L/h)	17.5 (5.78)	12.3 (6.90)

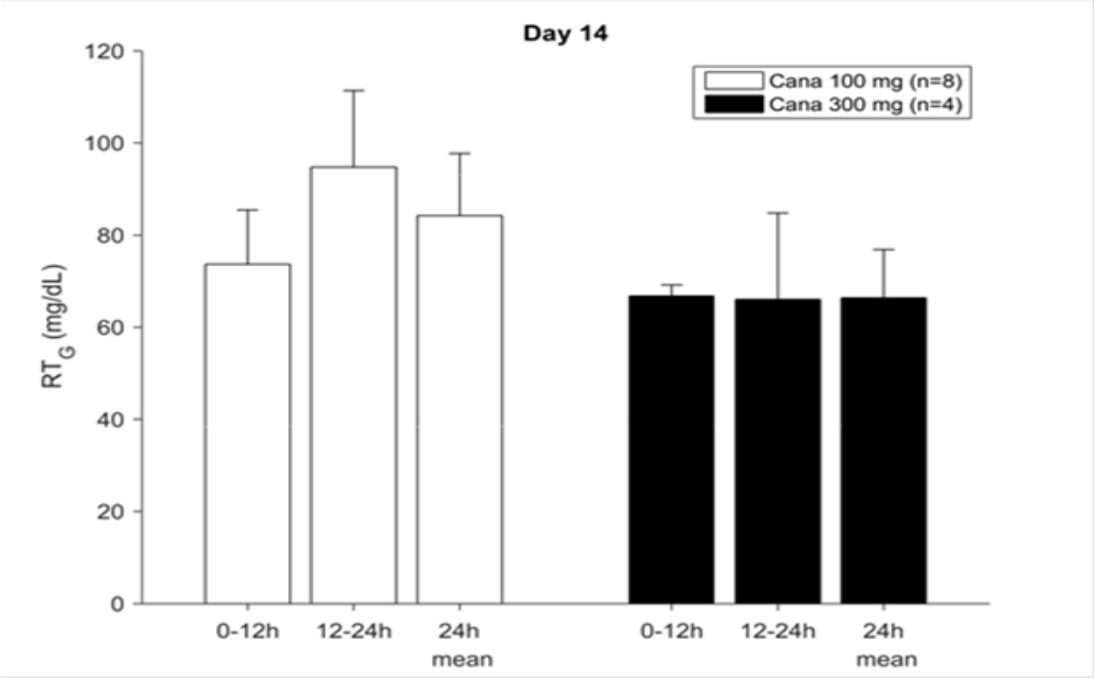
[a] Mean (range)

Pharmacodynamics

Renal Threshold for Glucose Excretion

Dose-dependent reductions in RTG were seen on Day 14. The 100-mg canagliflozin dose reduced mean RT_G to 74 mg/dL (4.11 mmol/L) over 0-12 hour, with a modest attenuation of the effect seen in the 12-24 hour period where mean RT_G was 95 mg/dL (5.27 mmol/L), giving a mean 24-hour mean RT_G of 85 mg/dL (4.72 mmol/L). With the 300 mg dose, mean RT_G was 67 mg/dL (3.72 mmol/L) over 0-12 hour and 72 mg/dL (4 mmol/L) over 12-24 hour, with mean 24-hour mean RT_G of 69 mg/dL (3.83 mmol/L). These results are consistent with findings in adult populations, in which the 100 mg dose gave near-maximal effects over the first 12 hour with a modest attenuation of the effect in the overnight period and doses of 300 mg or higher sustained near-maximal effects throughout the full 24 hours period.

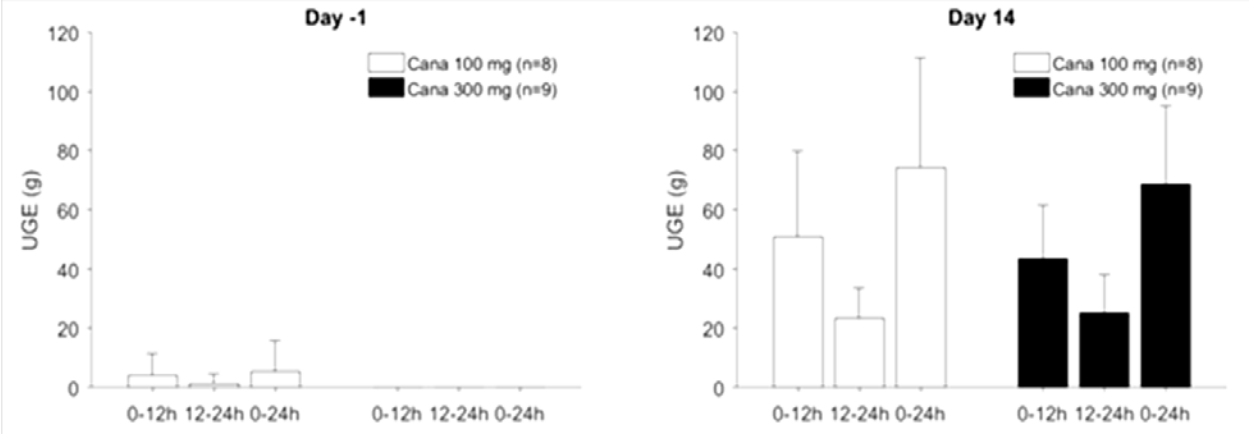
Mean (SD) RT_G Values on Day 14 After 100 mg (Left) and 300 mg (Right) of Canagliflozin



Urinary Glucose Excretion (UGE)

On Day -1, most subjects had only trace amounts of UGE (15 of the 17 subjects had UGE_{0-24h} <0.18 g); two subjects in the 100 mg cohort who had high plasma glucose concentrations had UGE of 13 g and 29 g. On Day 14, mean (SD) UGE_{0-24h} was 74 (37) g with the 100 mg dose and 69 (27) g with the 300 mg dose. With both doses, UGE was higher in the 0-12 hour period than in the 12-24 hour period as expected based on the higher plasma glucose concentrations during the daytime than in the overnight period. While the mean UGE seen in these subjects is modestly lower than seen in most of the Phase 1 studies in adult populations with T2DM (where mean UGE_{0-24h} with these doses ranged from 77-119 g), it is consistent with expectations based on the relatively low plasma glucose concentrations seen in the subjects in this study as evidenced by the mean RT_G values being suppressed to a range of approximately 65-95 mg/dL (3.6-5.3 mmol/L), which is similar to the effects seen in adult populations with T2DM.

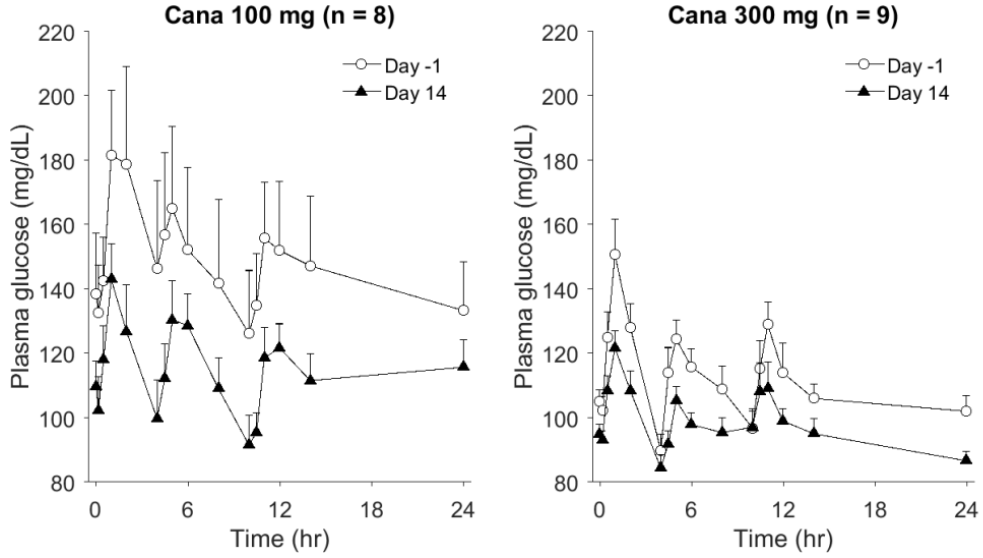
Mean (SD) UGE Values on Day-1 (Left) and Day 14 (Right) For Subjects Receiving 100 mg or 300 mg of Canagliflozin



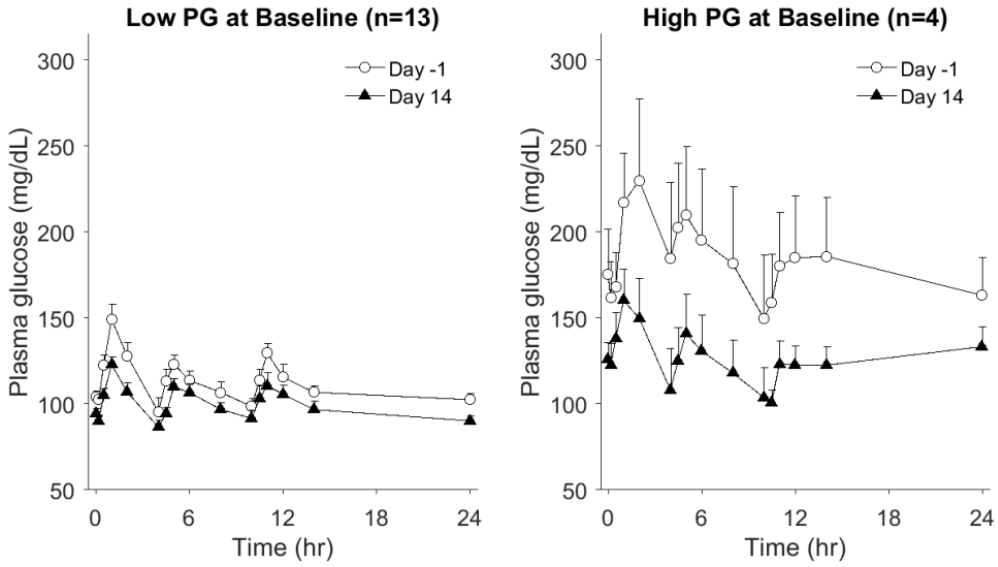
Plasma Glucose Concentrations

Both doses of canagliflozin reduced plasma glucose concentrations throughout the full 24 hour period, leading to a reduction in the mean plasma glucose (MPG_{0-4h} and MPG_{0-24h}) values between Day -1 and Day 14 in each group. Mean (SD) MPG_{0-4h} was reduced from 164 (69) mg/dL (9.1 mmol/L) to 120 (32) mg/dL (6.7 mmol/L) in the 100 mg cohort and from 119 (18) mg/dL (6.6 mmol/L) to 104 (12) mg/dL (5.8 mmol/L) in the 300 mg cohort. Mean (SD) MPG_{0-24h} was reduced from 147 (59) mg/dL (8.1 mmol/L) to 115 (23) mg/dL (6.4 mmol/L) in the 100 mg cohort and from 110 (11) mg/dL (6.1 mmol/L) to 96 (10) mg/dL (5.3 mmol/L) in the 300 mg cohort. Because many of the subjects started with plasma glucose concentrations that were below values typically found in subjects with type 2 diabetes, the magnitude of the mean reductions in plasma glucose were modest and an additional figure was generated to investigate the effects of canagliflozin in subjects with different levels of glucose control at baseline. Consistent with results seen in adult populations, relatively small reductions in plasma glucose were seen in subjects who had only modest hyperglycemia at baseline whereas much greater reductions in plasma glucose were seen in subjects with higher baseline plasma glucose concentrations.

Mean (+SE) Plasma Glucose Profiles on Day-1 and Day 14 after 100 mg (Left) or 300 mg (Right) of Canagliflozin



Mean (+SE) Plasma Glucose Profiles on Day-1 and Day 14 For Subjects With Baseline Fasting Plasma Glucose Levels Below (Left) and Above (Right) 126 mg/dL. Note that all 4 subjects in the higher baseline plasma glucose group were in the 100 mg cohort



ACCEPTABILITY OF THE TABLET

Results from the Day 14 acceptability questionnaire suggest either positive or neutral responses for a subject's perception of taste, smell, ability to swallow, or feelings after taking the canagliflozin dosage

PHARMACOGENOMIC RESULTS

DNA samples were analyzed for the *UGT1A9* and *UGT2B4* genes; specifically for the following variations which may be influential for canagliflozin pharmacokinetics: *UGT1A9 / UGT1A9 -2152C>T, UGT1A9 / UGT1A9 -275T>A, UGT1A9 / UGT1A9 *3, UGT1A9 / UGT1A9 *5, UGT2B4 / UGT2B4 *2*.

No subjects carried a UGT1A9*3 variant.

One subject carried the UGT1A9 –275T>A and –2152C>T polymorphisms, resulting in a designation of the 'H5 or H13' promotor haplotype. This subject's overall drug exposures (C_{max} and AUC) were similar to the group average values after receiving 300 mg. Two additional subjects were identified carrying a -275 T>A variation, but could not be assigned a composite genotype or haplotype. Similarly, these subject's overall drug exposures (C_{max} and AUC) were similar to the group average values after receiving 100 mg or 300 mg.

Two subjects were heterozygous (*1/*2) for the UGT2B4 *2 allele. These subject's overall drug exposures (C_{max} and AUC) were similar to the group average values after receiving 100 mg or 300 mg.

SAFETY RESULTS:

There were no deaths or serious adverse events reported during the study. None of the subjects discontinued the study medication due to an adverse event.

Overall, 9/17 (52.9%) subjects reported at least 1 treatment-emergent adverse event (TEAE) (4/8 [50.0%] subjects in the 100 mg group and 5/9 [55.6%] subjects in the 300 mg group). The most commonly reported TEAEs (≥10% subjects) by system organ class (SOC) were in gastrointestinal disorders (5/17 [29.4%]), followed by metabolism and nutrition disorders and skin and subcutaneous tissue disorders (2/17 [11.8%] each). The most frequently reported TEAE (≥2 subjects) by preferred term was nausea

(n=3); all other TEAEs were reported as single incident. Overall, the incidence of TEAEs was comparable between both the groups.

All the TEAEs reported were assessed by the investigator as mild in severity except for an event of metabolic acidosis, reported in one subject in the 100 mg group, which was moderate in severity. The majority of the TEAEs were judged by the investigator as "not" related or "doubtfully" related to the study treatment; two TEAEs of nausea and an event of vomiting were judged by the investigator as "possibly" related and the event of metabolic acidosis was judged as "very likely" related to the study treatment. All TEAEs had resolved or were resolving by the end of the study.

Three subjects were reported with events of clinical interest: One subjects (300 mg group) experienced four episodes of asymptomatic hypoglycemia based on fingerstick blood glucose measurements during the study, with resolution of each episode within less than 3.5 hours. These events were considered to be mild in intensity and doubtfully related to the study drug by the investigator. One subject (100 mg group) experienced an episode of metabolic acidosis on Day 14 based on a laboratory abnormality (described below). One subject (300 mg group) experienced a rash on Day 9. The investigator judged this event as contact dermatitis or eczema, mild in intensity, and doubtfully related to study drug. The rash was treated with a topical hydrocortisone cream and had resolved by the follow-up visit.

Overall, small group mean changes (ie, increases or decreases from baseline to Day 14) in certain laboratory analytes were observed. These changes were not considered to be clinically meaningful.

No clinically relevant changes in individual values for clinical laboratory analytes (hematology, serum chemistry, and urinalysis) were observed with the exception of one finding which was reported as a TEAE. One subject (100 mg group) had a decrease in serum bicarbonate from baseline on Day 14, which was below the lower limit of normal. At that time, the subject was asymptomatic, had normal glucose levels with no ketones present in the urinalysis. Based on the laboratory findings, the investigator reported this as a TEAE of metabolic acidosis. The subject's bicarbonate level was within the normal range at the follow-up visit. The event was considered to be moderate in intensity and very likely related to the study drug by the investigator.

No clinically relevant changes in group mean or individual subject values for vital signs, or ECG parameters were observed.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSION(S):

- A total of 17 subjects were enrolled, the majority were black or African American, female, with a median age of 15 years.
- The 3-fold range of BMI and body weight from subjects included within this study were notable, and are representative of adult BMI and body weight ranges.
- PK exposures in the 8 pediatric T2DM subjects receiving 100 mg once-daily and the 9 pediatric T2DM subjects receiving 300 mg once-daily doses of canagliflozin were consistent with those of adult subjects.
- The observed pharmacodynamic responses of reduction in RT_G, increases in UGE, and reductions in plasma glucose concentrations after receiving 100 mg once-daily or 300 mg once-daily doses of canagliflozin were consistent with those of adult subjects.
- Administration of canagliflozin 100 mg and 300 mg tablets appeared to be acceptable with reference to perception of taste, smell, ability to swallow, or feelings after taking the dosage in pediatric T2DM subjects in the age range studied in this study.

- Administration of canagliflozin 100 mg and 300 mg in pediatric T2DM subjects in the age range studied in this study was generally safe and well tolerated.

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