SYNOPSIS

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

Protocol No.: 28431754DIA1013

Title of Study: An Open-label Study to Evaluate the Pharmacokinetics of a Single Oral Dose of 300 mg JNJ-28431754 (Canagliflozin) in Subjects With Various Degrees of Impaired Hepatic Function Compared With Subjects With Normal Hepatic Function

EudraCT Number: Not applicable

NCT No.: NCT01186588

Clinical Registry No.: CR017227

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Study Center(s): Orlando Clinical Research Center (OCRC) - Orlando, FL and New Orleans Center for Clinical Research (NOCCR) – Knoxville, TN

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Phase of Development: 1

Objectives: The primary objective of this study was to characterize the pharmacokinetics (PK) of canagliflozin after administration of a single oral 300-mg dose of canagliflozin to subjects with mild or moderate hepatic impairment compared with subjects with normal hepatic function. The secondary objective was to characterize the PK of metabolites M7 and M5 after administration of a single oral 300-mg dose of canagliflozin to subjects with mild or moderate hepatic impairment compared with subjects with normal hepatic function. In addition, the safety and tolerability of canagliflozin were also assessed.

Methodology: This was an open-label, single-dose, multicenter PK study of canagliflozin in adult subjects with normal hepatic function and subjects with mild or moderate hepatic impairment. Subjects were classified into 1 of 3 hepatic function groups (normal hepatic function, mild hepatic impairment, and moderate hepatic impairment) on the basis of Child-Pugh classification. Group matching was applied to the hepatic function groups to ensure demographic comparability with respect to age and body weight. The study consisted of 3 phases: a Screening Phase of approximately 3 weeks (Day -23 through Day -3), an 8-day Open-label Treatment Phase (Day -2 through Day 6), and a Follow-up Phase (7 to 10 days after the last study-related procedure on Day 6). In the morning of Day 1 of the Open-label Treatment Phase, subjects received a single oral 300-mg dose of canagliflozin after an overnight fast of least 10 hours.

Number of Subjects (planned and analyzed): Planned: Approximately 24 medically stable men and women with normal hepatic function (healthy subjects) and with various degrees of hepatic impairment were to be enrolled in the study. Eight subjects were to be enrolled in each group (with at least 3 subjects of each gender per group). Dropouts were to be replaced with subjects (having similar age and body weight) to ensure that at least 8 subjects completed per hepatic function group. Analyzed: A total of

24 subjects (8 subjects per group) were enrolled in the 3 hepatic function groups. Safety and PK analyses included all 24 subjects enrolled in this study.

Diagnosis and Main Criteria for Inclusion: Men or women between 18 and 70 years of age, inclusive; body mass index (BMI) between 18 and 33 kg/m², inclusive were to be enrolled. Hepatic impairment was based on the Child-Pugh classification. Using this classification, subjects were grouped on the basis of 2 clinical features (encephalopathy and ascites) and 3 laboratory-based parameters (albumin, bilirubin, and International Normalized Ratio [INR]). Encephalopathy grading was done by the Principal Investigator according to the clinical staging and the Connect-the-numbers test. Subjects with mild and moderate hepatic impairment must have had a total Child-Pugh score of 5 or 6 and between 7 and 9, inclusive, respectively.

Test Product, Dose and Mode of Administration, Batch No.: Canagliflozin was administered orally as a single dose of a 300-mg over-encapsulated tablet (lot No.: 9DTK01X and expiration date: April 2011).

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

Duration of Treatment: The planned total duration of the study was approximately 39 days.

Criteria for Evaluation:

Pharmacokinetics

Serial blood samples were collected predose and up to 120 hours (Day 6) postdose for the determination of plasma concentrations of canagliflozin, and its metabolites (M7 and M5). Samples were analyzed using a validated, specific, and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The following plasma PK parameters of canagliflozin and its metabolites (M7 and M5) were determined for each hepatic function group: C_{max}, $C_{max,u}$, t_{max}, AUC_{last}, $AUC_{last,u}$, AUC_{∞}, $AUC_{\infty,u}$, $t_{1/2}$, Vd/F (parent only), Vd_u/F and CL/F (parent only), CL_u/F, CL_{NR}, M/P C_{max} ratio, and M/P AUC_{∞} ratio.

Urine samples were obtained at predetermined intervals up to 48 hours after dosing to determine concentrations of urine canagliflozin, and its metabolites (M7 and M5). The following urinary PK parameters were determined: Ae_{t1-t2}, Ae, Ae, %dose, and CL_R. CL_{CR} was calculated using the Cockcroft-Gault method.

The plasma protein binding (PPB) (% f_u and % f_b) of canagliflozin was determined by adding ^{14}[C] canagliflozin at a final concentration of 3.0 μg/mL to predose plasma samples from Day 1.

Safety

Safety and tolerability were evaluated throughout the study via assessment of adverse events (AEs), clinical laboratory tests, 12-lead electrocardiograms (ECGs), vital signs, physical examinations, and fluid intake and output. Hypoglycemia was monitored throughout the study.

Statistical Methods:

Sample size: Based on previous studies with canagliflozin, the intersubject coefficient of variation (CV) was estimated to be less than or equal to 30% for AUC and C_{max} of canagliflozin 300 mg for healthy subjects. Using an estimated intersubject CV of 40% for AUC and C_{max} of canagliflozin for the study population with different hepatic function, a sample size of 8 subjects per hepatic function group was determined to be sufficient for the point estimate of the geometric mean AUC and C_{max} of canagliflozin to fall within 71.6% and 139.7% of the true value with 95% confidence. As recommended in the Food and Drug Administration (FDA) guidance on hepatic impairment studies, a sample size of 8 subjects per hepatic function group was used in this study.

Pharmacokinetics: Individual and mean canagliflozin and its metabolites (M7 and M5) plasma concentration-time profiles were plotted for each hepatic function group. Plasma concentration data at

each timepoint and amounts recovered in urine during each collection interval were summarized. All PK parameters (total and free canagliflozin, if appropriate) of canagliflozin were summarized per hepatic function group.

The primary objective of the statistical analysis was to estimate the ratio of mean PK parameters (AUCs and C_{max}) of canagliflozin and its metabolites for each group of hepatic impairment subjects (mild and moderate) compared with subjects with normal hepatic function. An analysis of variance model was fitted to the log-transformed estimated AUCs and C_{max} with hepatic function as a fixed effect.

Safety: Safety was evaluated by examining the incidence and type of AEs and changes in clinical laboratory test values, physical examination results, 12-lead ECGs, and vital signs measurements beginning with the screening phase through to the final follow-up visit. Hypoglycemia was monitored throughout the study. Fluid intake and output was recorded.

RESULTS:

STUDY POPULATION:

A total of 24 subjects, (8 subjects in each hepatic function group) were enrolled and all the subjects completed the study as planned.

The groups were generally well balanced, with the normal hepatic function group modestly younger relative to the other groups, and the moderate hepatic impairment group with a modestly lower baseline body weight and BMI relative to the other groups. Overall, there were slightly more men than women and most subjects were white. The mean age across groups was 47 years (in the normal hepatic function group) to 55 years (in the moderate hepatic impairment group). The baseline Child-Pugh score in the hepatically impaired groups (mild and moderate) was consistent with the intended degrees of hepatic functional impairment to be studied.

PHARMACOKINETIC RESULTS:

Mean C_{max} and AUC_{∞} values for total plasma canagliflozin were similar across all hepatic function groups. Mean C_{max} and AUC_{∞} values for total plasma M7 increased with a decrease in hepatic function. The mean C_{max} value for total plasma M5 was lower in subjects with mild hepatic impairment and higher in subjects with moderate hepatic impairment, as compared to subjects with normal hepatic function, but AUC_{∞} increased with a decrease in hepatic function. Mean apparent $t_{1/2}$ values of total canagliflozin, total M7, and total M5 ranged from approximately 12.5 hours to 18.4 hours for all 3 hepatic function groups.

Less than 1.3% of the administered dose was excreted into urine as canagliflozin in the 3 hepatic function groups. The mean percentage of the dose recovered as M7 in urine increased with a decrease in hepatic function (22.9% and 34.5% in subjects with mild and moderate hepatic impairment, respectively, as compared to 17.2% in subjects with normal hepatic function). The mean percentage of the dose recovered as M5 in urine slightly increased with a decrease in hepatic function (9.36% and 10.0% in subjects with mild and moderate hepatic impairment, respectively, as compared to 8.17% in subjects with normal function).

For total M7, the molar corrected mean plasma metabolite-to-parent C_{max} and AUC_{∞} ratios increased with a decrease in hepatic function. The mean metabolite-to-parent molar ratios for total M5 C_{max} and AUC_{∞} were lower in subjects with mild hepatic impairment, and were greater in subjects with moderate hepatic impairment, as compared to subjects with normal hepatic function.

The geometric least squares means (LSMs) for total canagliflozin AUC_{∞} and C_{max} were similar for all hepatic function groups. The geometric LSMs for total M7 plasma AUC_{∞} and C_{max} increased in subjects with mild or moderate hepatic impairment as compared to subjects with normal hepatic function. The LSMs for total M5 AUC_{∞} and C_{max} were similar for subjects with mild hepatic impairment as compared

to subjects with normal hepatic function. For subjects with moderate hepatic impairment, there was a slight increase in geometric LSM AUC_{∞} and C_{max} relative to subjects with normal hepatic function.

The 90% confidence intervals (CIs) for the log-transformed difference in AUC_{∞} and C_{max} ratios of geometric means for total canagliflozin, total M7, and total M5 between the normal hepatic function group and mild or moderate hepatic impairment groups are summarized in the following table.

Geometric Mean Ratios and Their Associated 90% Confidence Intervals for Total Canagliflozin, Total M7 and Total M5 Pharmacokinetic Parameters in Subjects With Varying Degrees of Hepatic Function

			Total Canagliflozin		Total M7		Total M5	
Parameter	Hepatic Function	N	Geometric LSM	Ratio (90% CI)	Geometric LSM	Ratio (90% CI)	Geometric LSM	Ratio (90% CI)
C_{max} (ng/mL)	Normal	8	2765.43		1709.69		1381.73	
	Mild	8	2972.69	107.49 (84.17 , 137.28)	2308.25	135.01 (91.16 , 199.96)	1295.67	93.77 (65.01 , 135.26)
	Moderate	8	2649.06	95.79 (75.01 , 122.33)	2704.19	158.17 (106.79 , 234.26)	1591.43	115.18 (79.85 , 166.13)
AUC_{∞} (ng.h/mL)	Normal	7[a]	23760.81		17943.73		17815.40	
	Mild	8	26033.81	109.57 (85.84 , 139.84)	28396.22	158.25 (110.80 , 226.03)	18758.13	105.29 (72.11 , 153.73)
	Moderate	8	26334.03	110.83 (86.83 , 141.46)	38254.72	213.19 (149.26 , 304.51)	24738.95[b]	138.86[b] (93.93 , 205.28)[b]

[a] n=7, as Subject 101332 was excluded from the descriptive statistics for parameters that were estimated based on the terminal phase due to unacceptable variability in the terminal phase

[b] n=7, as Subject 101320 was excluded from the descriptive statistics for parameters that were estimated based on the terminal phase due to unacceptable variability in the terminal phase

NOTE: Data were analyzed on natural log scale, but results are back-transformed to original scale.

NOTE: Ratio = Impaired/Normal

The percentage of canagliflozin unbound to plasma proteins was similar in subjects with normal hepatic function and in subjects with mild hepatic impairment, but was approximately 20% greater in subjects with moderate hepatic impairment. Concentrations of albumin and α-1-acid glycoprotein (AGP) were also similar in subjects with normal hepatic function and in subjects with mild hepatic impairment, but were approximately 11% lower and 14% lower, respectively, in subjects with moderate hepatic impairment.

The LSMs for unbound canagliflozin $AUC_{\infty,u,}$ and $C_{max,u}$ were slightly greater (approximately 10%) for subjects with mild hepatic impairment, as compared to subjects with normal hepatic function. For subjects with moderate hepatic impairment, there was a slight increase in geometric LSM $C_{max,u}$ (14%) and AUC_{∞} (31%) relative to subjects with normal hepatic function.

Geometric Mean Ratios and Their Associated 90% Confidence Intervals for Unbound Canagliflozin Pharmacokinetic Parameters Following Administration of Canagliflozin in Subjects With Varying Degrees of Hepatic Function

(Study: 28431754DIA1013: Pharmacokinetic Data Analysis Set)

Parameter	Hepatic Function	N	Geometric LSM	Ratio (Impaired/Normal)	90% CI
$C_{max,u}$ (ng/mL)	Normal	8	28.17		
	Mild	8	30.61	108.69	(88.46 , 133.53)
	Moderate	8	32.09	113.93	(92.73 , 139.97)
$AUC_{\infty,u}$ (ng.h/mL)	Normal	7[a]	242.73		
	Mild	8	268.12	110.46	(83.97 , 145.30)
	Moderate	8	319.02	131.43	(99.91 , 172.89)

[a] n=7, as Subject 101332 was excluded from the descriptive statistics for parameters that were estimated based on the terminal phase due to unacceptable variability in the terminal phase (r^2_{adj}: 0.8322).

Key: CI = confidence intervals, N = total sample size, LSM= Least-Squares Mean

NOTE: Data were analyzed on natural log scale, but results are back-transformed to original scale.

SAFETY RESULTS:

Adverse Events: Overall, the incidence of subjects with 1 or more treatment-emergent adverse events (TEAEs) in each group in this study was low: 4 subjects (50%) with mild hepatic impairment, 2 subjects (25%) with moderate hepatic impairment, and 1 subject (13%) with normal hepatic function. Treatment-emergent adverse events of the nervous system disorders system organ class (SOC) (headache) were the most common in the mild and moderate hepatic impairment groups. Only 1 specific TEAE was reported in more than 1 subject (headache reported in 2 subjects). All TEAEs except 1 were mild in intensity: a subject in the normal hepatic function group had a TEAE of heat exhaustion on Day 12 (11 days postdose), severe in intensity, considered not related to the study drug by the investigator. No TEAEs were considered by the investigator to be probably or very likely related to the study drug. Those TEAEs assessed as possibly related to study drug were: headache, hyperhidrosis, upper abdominal pain, nausea, and vomiting. There were no deaths, other serious adverse events (SAEs), persistent AEs, or discontinuations due to AEs reported in this study. No hypoglycemic episodes were reported in the study.

Safety Laboratory Tests: A small mean increase (approximately 5%) from baseline (Day -2) in hemoglobin (Hb) concentration was noted in the normal hepatic function group on Day 4, which tended to return to the baseline value at the end-of-study visit. No notable changes were observed in the hepatically impaired groups. No notable changes in coagulation parameters (including activated partial thromboplastin time [PTT] and prothrombin INR) and other hematology parameters were seen.

No notable changes or trends for changes were observed for any liver function test. Mean lactic acid dehydrogenase (LDH) levels decreased in all groups on Day 4 compared to baseline (Day -2): (approximately 25%, 22%, and 14% in the normal hepatic function, mild hepatic impairment, and moderate hepatic impairment groups, respectively).

Mean plasma urate levels decreased in all groups on Day 4 compared to baseline (Day -2) (approximately 20%, 30%, and 8% in normal hepatic function, mild hepatic impairment, and moderate hepatic impairment groups, respectively), with levels near baseline at the end-of-study visit. A slight increase in serum creatinine in the normal hepatic function group was observed, with a slight increase in blood urea nitrogen (BUN) only seen in the moderate hepatic impairment group.

A small decrease (approximately 26%, 56%, and 44% in normal hepatic function, mild hepatic impairment, and moderate hepatic impairment groups, respectively) in mean plasma creatine kinase (CK) levels on Day 4 compared to baseline (Day -2) was noted in all groups, with values generally similar to baseline at the end-of-study visit.

No notable or consistent changes in fluid intake or urinary output were observed.

No laboratory abnormalities were reported as TEAEs

Other Safety Assessments: No clinically relevant changes in mean body weight or BMI were observed in any hepatic function group.

Small decreases from baseline in mean sitting systolic blood pressure (SBP) (from 3.5 mm Hg to 5.0 mm Hg) were observed in the normal hepatic function group on Day 1 through Day 3. No consistent changes in the sitting SBP were apparent in the hepatically impaired groups (mild and moderate). Small, but more variable, decreases were also observed in mean sitting diastolic blood pressure (DBP) in the normal hepatic function group, with no notable changes in the hepatically impaired groups.

A small increase from baseline in the mean sitting pulse rate (ranging from 6.6 beats per minute [bpm] to 7.8 bpm) was observed in all hepatic function groups at 2 hours postdose on Day 1, with small increases also observed at some later timepoints in all hepatic function groups.

No clinically significant ECG and physical examination abnormalities were recorded during the study.

STUDY LIMITATIONS: The limitations of the present study included its small sample size (8 subjects per group) and the lack of a placebo group.

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