SYNOPSIS

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

Protocol No.: 28431754DIA1003

Title of Study: An Open-Label, Single-Dose Study to Evaluate Canagliflozin Pharmacokinetics, Pharmacodynamics and Safety in Non-Diabetic Subjects With Varying Degrees of Renal Function

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Study Period: 10 March 2008- 24 November 2008

Phase of Development: 1

Objectives: The primary objectives of this study were to characterize the single-dose pharmacokinetics and pharmacodynamics of canagliflozin after oral administration to nondiabetic subjects with varying degrees of renal function and to subjects with ESRD, requiring HD. The secondary objectives of this study were to compare the pharmacokinetics and pharmacodynamics of canagliflozin in nondiabetic subjects with varying degrees of renal insufficiency and ESRD to a control group of healthy subjects.

Methods: This was an open-label, single-dose, multicenter, parallel-group study. Forty medically stable nondiabetic men and women with varying degrees of renal function were enrolled. Subjects were assigned to 1 of 5 groups (8 subjects per group) as determined by creatinine clearance. Subjects in Groups 1 to 4 received 1 treatment (a single dose) of canagliflozin. Subjects in Group 5 received 1 treatment sequence consisting of a single oral dose (Treatment A, post-dialysis) of canagliflozin followed by a second single oral dose (Treatment B, pre-dialysis) approximately 10 days later.

Number of Subjects (planned and analyzed): All 40 eligible subjects were enrolled, received the planned dose of study drug (2 doses in Group 5) and were included in the safety analysis set.

Diagnosis and Main Criteria for Inclusion: Forty medically stable men and women with varying degrees of renal function, between 18 and 79 years of age, inclusive; body mass index between 20 and 40 kg/m², inclusive, were enrolled. Subjects must have had stable renal function; subjects receiving HD must have been receiving the same dialysis treatment and schedule for at least 1 month.

Criteria for Evaluation: Blood samples were collected for pharmacokinetics and pharmacodynamics (plasma glucose) and urine samples for pharmacodynamics (urinary glucose excretion [UGE]) and safety, as described below.

Pharmacokinetics: For all subjects, blood samples (3 mL each) for determination of canagliflozin plasma concentrations were collected at the time points indicated in the Time and Events Schedule in the study protocol. For subjects in Group 5, Treatment B, additional paired blood samples (3 mL each) from the hemodialyzer of predialyzer (arterial) and postdialyzer (venous) blood were collected every hour for plasma drug levels. In addition, blood samples (2 mL) predialyzer and postdialyzer paired samples were obtained every hour from the arterial and venous lines of the dialysis equipment to determine glucose values to allow for calculation of the extraction ratio of the hemodialyzer and to compare with the extraction ratio of the study drug. Urine was collected over the intervals for subjects in Groups 1 to 4 and for subjects in Group 5 (who were able to produce urine) at specified time points indicated in the Time and Events Schedule that follows the synopsis in the study protocol. Dialysate fluid was obtained from subjects in Group 5, Treatment B, at hourly intervals during the 4-hour HD session at specified times indicated in the Time and Events Schedule that follows the synopsis in the study protocol. Each hourly interval was thoroughly mixed and a 4-mL aliquot was removed. The exact dates and times of blood sampling, dialysate flow, blood flow rate, dialysate volume collected, and ultrafiltrate rate was noted in the CRF.

Pharmacodynamics: Urine samples were collected for assessment of UGE at selected time intervals on Day −1 (baseline) and from Days 1 to 4 at selected time intervals as described in the Time and Events Schedule in the study protocol. All subjects had blood samples (2 mL) for measurement of plasma glucose collected on Day –1 (baseline) from immediately before breakfast and at selected time points up to 16 hours after a standard breakfast and again on Day 1 at predetermined time points as described in the Time and Events Schedule .

Pharmacogenomics: A 10-mL blood sample was collected from subjects who consented to take part in the pharmacogenomic component of the study at the time point indicated in the Time and Events Schedule that follows the synopsis in the study protocol.

Safety: Safety and tolerability were evaluated via an assessment of adverse events monitored continuously throughout the study, and clinical laboratory tests (hematology, serum chemistry, and urinalysis), 12-lead ECGs (RR, PR, QRS, QT, and QT corrected intervals), heart rate, vital signs (pulse, blood pressure, respiratory rate, tympanic or oral temperature) and physical examinations. Hypoglycemia was monitored throughout the study.

Statistical Methods:

Sample size: Using an estimated intersubject coefficient of variation of 30% for AUCs and C_{max} of canagliflozin, a sample size of 6 subjects per renal impairment group would be sufficient for the point estimate of the geometric mean AUCs and C_{max} to fall within 73.0% and 137.0% of the true value with 95% confidence. Using an estimated intersubject coefficient of variation of 24% for UGE_{0-24} of canagliflozin, a sample size of 6 subjects per renal impairment group would be sufficient for the point estimate of the arithmetic mean UGE_{0-24} to fall within 74.8% and 125.2% of the true value with 95% confidence.

Pharmacokinetics: The primary parameters of interest for the statistical analysis were the log-transformed estimated AUCs (AUC_{last}, AUC_{∞}) and C_{max}. Using the estimated least squares means and intersubject variance, the point estimate and 90% confidence intervals for the difference in means on a log scale between each renal function group and the normal renal function group was constructed.

Pharmacodynamics: The analysis of 24-hour UGE (UGE_{0-24}, UGE_{24-48}, UGE_{48-72}) and plasma glucose AUC ($glucose_{AUC4}$, $glucose_{AUC24}$) was calculated and summarized using descriptive statistics before and after JNJ-28431754 dose administration.

Safety: Safety was evaluated by examining the incidence and type of adverse events, and changes in clinical laboratory test values, physical examination results, 12-lead ECGs, and vital signs measurements from the screening phase through to study completion.

RESULTS:

All 40 eligible subjects were enrolled, received the planned dose of study drug (2 doses in Group 5). All 40 enrolled subjects completed the study.

Demographic and Baseline Characteristics
(STUDY 28431754DIA1003: Safety Analysis Set)

	Normal Renal Function (N=8)	Mild Impairment (N=8)	Moderate Impairment (N=8)	Severe Impairment (N=8)	ESRD (N=8)	Total (N=40)
Race, n (%)						
White	7 (88)	6 (75)	7 (88)	7 (88)	2 (25)	29 (73)
Black or African American	1 (13)	2 (25)	1 (13)	1 (13)	6 (75)	11 (28)
Sex, n (%)						
Male	5 (63)	3 (38)	2 (25)	5 (63)	7 (88)	22 (55)
Female	3 (38)	5 (63)	6 (75)	3 (38)	1 (13)	18 (45)
Age (yrs)						
Mean	52.0	59.8	62.6	61.3	43.8	55.9
SD	8.30	16.65	15.46	11.55	7.30	13.79
Median	50.5	67.0	67.5	63.5	44.5	56.5
Minimum	42	31	29	45	31	29
Maximum	65	75	77	77	56	77
Weight (kg)						
Mean	92.53	70.05	77.74	72.73	103.96	83.40
SD	8.880	8.447	15.217	12.149	22.896	18.959
Median	92.30	67.25	74.90	74.60	105.45	81.40
Minimum	82.4	61.0	54.0	51.5	70.0	51.5
Maximum	105.9	85.4	97.3	88.1	137.7	137.7
Height (cm)						
Mean	172.36	165.21	166.73	171.04	177.65	170.60
SD	10.036	10.618	10.926	7.792	7.872	10.083
Median	173.00	162.15	164.55	171.00	177.00	170.00
Minimum	157.4	154.0	152.5	157.0	169.4	152.5
Maximum	185.4	185.4	188.0	184.0	194.3	194.3

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS: Data from 40 subjects with renal function ranging from normal to ESRD (requiring HD) who received a single 200 mg oral dose of canagliflozin were included in the pharmacokinetic analysis.

Canagliflozin was rapidly absorbed as seen by most subjects having measurable plasma concentrations 30 minutes after study drug administration. At all time points, mean plasma concentrations of canagliflozin were higher in subjects with mild, moderate and severe renal impairment compared to that of the normal group. In contrast, the mean plasma concentration-time profiles in ESRD subjects dosed 2 hours before (pre-dialyses) or 1 hour after (post-dialyses) undergoing a 4-hour HD session were comparable to that of the normal group.

Half-life ($t_{1/2}$) was slightly longer in subjects with mild, moderate and severe renal impairment when compared to the normal renal function group. For the ESRD subjects, $t_{1/2}$ was also longer in the pre-dialysis group, but it was similar for the post-dialysis group when compared to the normal renal function group. Mean apparent oral clearance (CL/F) values were lower in subjects with mild, moderate and severe renal impairment compared to normal subjects. Mean CL/F appeared to be unaffected by the timing of a 4-hour HD session relative to dosing in ESRD subjects and was similar to the normal subjects. Apparent volume of distribution was similar for the pre- and post-dialyses groups when compared to the normal renal function group.

Mean renal clearance (CL_R) and urinary recovery of canagliflozin were low and decreased with reduced renal function. Overall, urinary recovery of canagliflozin was <1% of the administered dose across all renal function groups. In addition, following a 4-hour HD session, <1% of the administered dose was recovered in the dialysate fluid.

Mean C_{max} values increased for subjects with mild, moderate, and severe impairment compared to the normal renal function group. Similarly, mean AUC_∞ values increased for subjects with mild, moderate and severe impairment, respectively, compared to the normal renal function group Exposure (AUC and C_{max}) in ESRD subjects dosed 2 hours before (pre-dialysis) or 1 hour after (post-dialysis) undergoing a 4-hour HD session were comparable to that of the normal group. Generally, mean AUC and C_{max} values were comparable for the pre-dialysis group compared to the post-dialysis group.

The mean weight-normalized C_{max} values were comparable in subjects with moderate and severe renal impairment compared to the normal renal function group and decreased for subjects with mild renal impairment. Weight normalized mean AUC_∞ values decreased for subjects with mild renal impairment, and increased in subjects with moderate and severe impairment, respectively, compared to the normal renal function group. Exposure (AUC and C_{max}) in ESRD subjects dosed 2 hours before (pre-dialysis) or 1 hour after (post-dialysis) undergoing a 4-hour HD session increased compared to that of the normal group. Generally, mean weight-normalized AUC and C_{max} values were comparable for the pre-dialysis group compared to the post-dialysis group.

Mean plasma concentrations of metabolites M7 and M5 increased rapidly in each renal function group, with most subjects having measurable concentrations 30 minutes after dosing. As with the parent compound, plasma concentrations of M7 and M5 were quantifiable at 96- (normal renal function) and 120-hours post-dose for most subjects impaired renal functions.

Median t_{max} values for both the metabolites were similar across all groups except for metabolite M5 in the ESRD groups, which was delayed . Mean C_{max} and AUC values for both metabolites were higher in subjects with renal impairment when compared to that of the normal group.

Metabolite-to-parent molar ratios of C_{max} ranged between 0.63 to 1.22 and 0.40 to 1.04 for M7 and M5, respectively while molar ratios for AUC ranged between 0.82 to 1.84 and 0.70 to 1.84 for M7 and M5, respectively. For both metabolites these values generally increased with decreasing renal function for both metabolites.

In renally impaired subjects, mean $t_{1/2}$ values for metabolites M7 and M5 were generally prolonged except for M7 post-dialysis, which was similar to the normal renal function group.

The amount of each metabolite eliminated in urine decreased for M7 and M5 in subjects with normal renal function and increasing degrees of renal impairment. M7 exposure increased after administration of canagliflozin for subjects with mild, moderate or severely impaired renal functions. The mean C_{max} increased for subjects with mild, moderate, severe impairment and ESRD (post-dialysis) and ESRD (pre-dialysis), respectively, when compared to the normal renal function group.

M5 exposure increased after administration of canagliflozin for subjects with mild, moderate or severely impaired renal functions. Mean C_{max} increased for subjects with mild, moderate, severe impairment and ESRD (post-dialysis) and ESRD pre-dialysis), respectively when compared to the normal renal function group.

M7 exposure increased after administration of canagliflozin for subjects with mild, moderate or severely impaired renal functions. Weight normalized mean AUC_{∞} increased for subjects with mild, moderate and severe impairment, and ESRD (post-dialysis) and ESRD (pre-dialysis) respectively, when compared to the normal renal function group. The mean C_{max} increased for subjects with mild, moderate, severe impairment and ESRD (post-dialysis) and ESRD (pre-dialysis), respectively, when compared to the normal renal function group.
M5 exposure increased after administration of canagliflozin for subjects with mild, moderate or severely impaired renal functions. Weight normalized mean AUC_{∞} decreased for subjects with mild renal impairment and increased in subjects with, moderate and severe impairment and ESRD (post-dialysis) and ESRD (pre-dialysis), respectively when compared to the normal renal function group. Weight normalized mean C_{max} increased for subjects with mild, moderate, severe impairment and ESRD (post-dialysis) and ESRD (pre-dialysis), respectively when compared to the normal renal function group.

Canagliflozin was negligibly removed during a 4-hour HD session as indicated by a low ER (<0.047). Mean Q_B and CL_{HD} appeared to increase slightly over the 4-hour HD session.

Protein binding, total protein, and albumin were similar across all renal function groups including HD subjects. Alpha-1-AGP increased with decreasing renal function.

Individual UGE_{24} changes from baseline on Day 1 increased vs. Day -1 and decreased with a decrease in renal function. During the first 24 hours after dosing (Day 1), mean 24-hour UGE change from baseline values significantly decreased with decreasing renal function compared to subjects with normal renal function. A similar trend was also observed on Day 2 and Day 3 after dose administration.

Urine volumes were slightly higher for the normal renal function subjects throughout the study compared to subjects with impaired renal function. Within each study day, urine volumes were similar across the mild to severely impaired renal function groups.

Mean plasma glucose AUC_{0-4} and AUC_{0-24} values were comparable to baseline (Day -1) in all groups evaluated.

In subjects with normal renal function or mild impairment, the R_T was lowered to approximately 60 to 75 mg/dl with treatment, whereas in subjects with moderate or severe renal impairment, the R_T was only lowered to approximately 90 to 100 mg/dl with treatment.

SAFETY RESULTS: In total, 14 subjects (35%) experienced at least one treatment-emergent adverse event. The most common adverse events were nausea (4 subjects, 10%), dizziness (3 subjects, 7.5%), abdominal pain upper (2 subjects, 5%) and back pain (2 subjects, 5%).

The incidence of treatment emergent adverse events in the treatment groups ranged from 0 to 50%. The incidence, pattern, and severity of adverse events did not appear to differ across groups from subjects with normal renal function to subjects with severe renal impairment.

Hemoglobin decreased for 1 subject (200004) in the mild impairment group. It was considered by the investigator as to be mild in intensity and very likely related to study medication. One subject (100018) in the normal renal function group experienced nausea and dizziness that were mild in intensity and were considered by the investigator to be probably related to study medication. All other adverse events were possibly, doubtfully or unrelated to study drug administration.

There were no deaths, serious adverse events, or subjects who reported persistent adverse events. There were no reported hypoglycemic events and no subjects who were enrolled in the study discontinued due to adverse events.

Treatment-Emergent Adverse Events by Body system or Organ Class and Dictionary-derived Term
(Study 28431754DIA1003: Safety Analysis Set)

Body System Or Organ Class Dictionary-Derived Term	Normal Renal Function (N=8) n (%)	Mild Impairment (N=8) n (%)	Moderate Impairment (N=8) n (%)	Severe Impairment (N=8) n (%)	ESRD-Post HD (N=8) n (%)	ESRD-Pre HD (N=8) n (%)	Total (N=40) n (%)
Total no. subjects with adverse events	2 (25.0)	4 (50.0)	2 (25.0)	4 (50.0)	2 (25.0)	0	14 (35.0)
Gastrointestinal disorders	1 (12.5)	2 (25.0)	2 (25.0)	2 (25.0)	1 (12.5)	0	8 (20.0)
Abdominal discomfort	0	0	0	1 (12.5)	0	0	1 (2.5)
Abdominal pain upper	0	1 (12.5)	0	0	1 (12.5)	0	2 (5.0)
Diarrhea	0	0	1 (12.5)	0	0	0	1 (2.5)
Nausea	1 (12.5)	1 (12.5)	1 (12.5)	1 (12.5)	0	0	4 (10.0)
General disorders and administration site conditions	1 (12.5)	0	0	2 (25.0)	1 (12.5)	0	4 (10.0)
Asthenia	0	0	0	0	1 (12.5)	0	1 (2.5)
Fatigue	0	0	0	1 (12.5)	0	0	1 (2.5)
Gait disturbance	0	0	0	1 (12.5)	0	0	1 (2.5)
Vessel puncture site hematoma	1 (12.5)	0	0	0	0	0	1 (2.5)
Investigations	0	1 (12.5)	0	0	0	0	1 (2.5)
Hemoglobin decreased	0	1 (12.5)	0	0	0	0	1 (2.5)
Musculoskeletal and connective tissue disorders	0	2 (25.0)	0	0	0	0	2 (5.0)
Back pain	0	2 (25.0)	0	0	0	0	2 (5.0)
Nervous system disorders	1 (12.5)	0	0	2 (25.0)	0	0	3 (7.5)
Dizziness	1 (12.5)	0	0	2 (25.0)	0	0	3 (7.5)
Skin and subcutaneous tissue disorders	0	1 (12.5)	0	0	0	0	1 (2.5)
Cold sweat	0	1 (12.5)	0	0	0	0	1 (2.5)

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

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