SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development
Name of Finished Product	Not Available
Name of Active Ingredient(s)	JNJ-28431754

Protocol No.: 28431754DIA1008

Title of Study: A Single-Dose, Open-Label, Randomized, Two-Way, Cross-Over Study to Assess the Pharmacokinetics and Pharmacodynamics of JNJ-28431754 in Healthy Indian Subjects

Principal Investigator: Charu Gautam, MD, DNB, Lambda Therapeutics Research Ltd, [redacted], India.

Publication (Reference): None

Study Period: 06 August 2008 to 09 September 2008; database lock: 31 October 2008

Phase of Development: 1

Objectives: The primary objective of this study was to characterize the single-dose pharmacokinetics (PK) and pharmacodynamics (PD) of 2 oral doses JNJ-28431754 (200 and 300 mg) after oral administration to healthy Indian subjects. The safety and tolerability of JNJ-28431754 were also assessed.

This study explored the PK and PD parameters in association with polymorphisms in genes in healthy subjects that may also be found in subjects with type 2 diabetes mellitus (T2DM) and/or obesity.

Methods: This was an open-label, randomized, single-center, single-dose, 2-way cross-over study. Approximately 16 healthy Indian men and women were enrolled and randomized to receive 2 single oral doses of JNJ-28431754 (200 and 300 mg). The study consisted of 3 phases; a single screening phase of up to 19 days, a baseline phase of 2 days per period, and an open-label treatment phase that included 2 periods (Periods 1 and 2) consisting of 4 days each separated by a 14-day washout between dosing days (Day 1) of each period. Subjects were randomized prior to dosing on Day 1 of Period 1 to receive each of the following treatments in the order determined by randomization: Treatment A: subjects received JNJ-28431754 as one 200-mg tablet 10 minutes prior to breakfast, and Treatment B: subjects received JNJ-28431754 as one 300-mg tablet 10 minutes prior to breakfast. The total duration of the study was approximately 45 days.

Number of Subjects (planned and analyzed): Planned: Sixteen subjects, including at least 5 women, were to be enrolled to ensure that at least 12 subjects completed the study. Analyzed: Sixteen subjects were enrolled, and 15 subjects were randomized and received at least 1 dose of study drug. One subject was not randomized. Of the 15 randomized subjects, 14 subjects completed the study. One subject was withdrawn from the study. All 15 randomized subjects were analyzed for safety, PK and PD.

Diagnosis and Main Criteria for Inclusion: Healthy Indian men and women between 18 and 55 years of age, inclusive; body mass index (BMI) between 18 and 35 kg/m², inclusive and a body weight of not less than 50 kg, glomerular filtration rate (GFR) ≥ 90 mL/min/1.73 m^2; with a screening FPG of <100 mg/dL and a screening plasma glucose (2-hour sample) during an oral glucose tolerance test of <140 mg/dL.

Test Product, Dose and Mode of Administration, Batch No.: JNJ-28431754 was administered orally as a single dose of 200-mg (lot No: PD2602) and 300-mg (lot No: PD2741) tablets.

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

Duration of Treatment: Subjects received single oral doses of 200-and 300-mg JNJ-28431754. The treatment was administered in 2 periods consisting of 4 days each separated by a 14-day washout between dosing days (Day 1) of each period.

Criteria for Evaluation: Blood and urine samples were collected for PK, PD, and safety, as described below.

Pharmacokinetics: Blood samples for pharmacokinetic analyses were obtained predose and up to 72 hours (Day 4) postdose during open-label treatment Periods 1 and 2. Plasma samples were analyzed to determine concentrations of JNJ-28431754 using a validated, specific and sensitive liquid chromatography coupled to mass spectrometry/mass spectrometry (LC-MS/MS) method under the supervision of the Sponsor's Bioanalytical Laboratory Department of Bioanalysis. Pharmacokinetic parameters for JNJ-28431754 estimated from plasma included: C_{max}, t_{max}, AUC_{0-24h}, AUC_{last}, AUC_{∞}, $t_{1/2}$, λ_z.

Pharmacodynamics: Blood samples for plasma glucose, insulin and C-peptide were collected during both open-label treatment periods up to 72 hours postdose. AUC_{0-4h} was determined as appropriate for plasma glucose, insulin, and C-peptide.

Urine samples were collected in both the open-label treatment periods for a period of 24 hours prior to dosing (Day –1) and up to 72 hours postdose for assessment of urine glucose excretion over 24 hours (UGE_{24}).

The relationship between renal threshold (R_T) and plasma drug levels was evaluated to determine the total UGE using the trapezoidal method. The value of R_T was determined so that this integral was equal to the measured UGE over the corresponding time interval (Polidori, manuscript in preparation). GFR was estimated using the modification of diet in renal disease (MDRD) formula.

Pharmacogenomics: A mandatory pharmacogenomic blood sample (10 mL) was collected at baseline (Period 1 only).

Safety: Safety and tolerability were assessed from screening through to study completion. Adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), 12-lead electrocardiograms (ECGs) (RR, PR, QRS, QT, QT corrected intervals, according to Fredericia [QTcF] and Bazett [QTcB]), heart rate), vital signs (pulse, blood pressure, respiratory rate, oral temperature), and physical examinations were evaluated. Parameters such as 24-hour urinary glucose, creatinine, electrolytes, and albumin for the assessment of PD and safety/ tolerability were evaluated. Hypoglycemia was monitored throughout the in-house period.

Statistical Methods:

Sample size: Using an estimated intersubject coefficient of variation of 31% for AUC and C_{max} of JNJ-28431754, a sample size of 12 subjects was determined to be sufficient for the point estimate of the geometric mean AUC and C_{max} of JNJ-28431754 to fall within 82.1% and 121.8% of the true value with 95% confidence. Using an estimated intersubject coefficient of variation of 23% for AUC and C_{max} of JNJ-28431754, a sample size of 12 subjects was determined to be sufficient for the point estimate of the arithmetic mean UGE_{24} and arithmetic mean change from baseline UGE_{24} to fall within 85.4% and 114.6% of the true value with 95% confidence. Sixteen subjects were to be enrolled to ensure that 12 subjects completed all study procedures during all treatment periods, including the 72-hour PK blood sample collection on Day 4 of Period 2, and the end-of-study evaluations.

Pharmacokinetics: Plasma concentration data at each time-point were summarized and 90% confidence interval (CI) for the ratio of mean dose-normalized (to 200 mg) PK parameters (AUC and C_{max}) of 300 mg to 200 mg were constructed using the estimated least squares means and intrasubject variance from a mixed effects model.

Pharmacodynamics: UGE_{24} and plasma glucose ($AUC_{0-4h,}$), insulin (AUC_{0-4h}), and C-peptide (AUC_{0-4h}) were summarized at baseline in each period, and after study drug administration. For each PD parameter,

90% CI for the difference of means between 200-and 300-mg JNJ-28431754 doses were constructed using the estimated least squares means and intrasubject variance from a mixed effects model.

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, including the washout interval. Hypoglycemia was monitored throughout the in-house period.

RESULTS:

A total of 15 healthy Indian men and women aged 22 to 43 years (inclusive), with a BMI between 21 and 27 kg/m^2 (inclusive) and a body weight between 52 and 75 kg, were randomized. Fourteen of the 15 eligible subjects completed the study. One subject was withdrawn from the study due to a positive urine pregnancy test and serum beta-human chorionic gonadotropin test.

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS: Following oral administration at each dose level, the mean plasma JNJ-28431754 concentrations increased rapidly with median t_{max} values of 1.50 hours. The mean C_{max} and AUC increased with the dose, while t_{max} and $t_{1/2}$ were independent of dose. After accounting for body weight, C_{max} and AUC were similar in Indian subjects compared to Western subjects for both the 200-and 300-mg doses.

Mean (±SD) Body-Weight Normalized Pharmacokinetic Parameters Across Studies
(Study 28431754DIA1008: Pharmacokinetics Data Analysis Set)

	JNJ-28431754			
	----------200 mg----------		----------300 mg----------	
PK Parameters	DIA-1008 (n=15)	DIA-1003 (n=8)	DIA-1008 (n=14)	DIA-1010 (n=56)
C_{max} (ng/mL)	1792 (430)	1475 (669)	2789 (941)	2408 (565)
C_{max} (ng/mL)[a]	1511 (304)	1897 (754)	2365 (696)	2312 (499)
AUC_{0-24h} (ng.h/mL)	14524 (2605)	10825 (2591)	21948 (4268)	18857 (4094)
AUC_{0-24h} (ng.h/mL)[a]	12309 (2006)	14164 (2796)	18859 (3788)	18128 (3710)
AUC_{∞} (ng.h/mL)	18706 (3818)	14345 (3605)	28207 (5901)	NC
AUC_{∞} (ng.h/mL)[a]	15892 (3190)	18836 (4261)	24320 (5600)	NC

[a] body weight normalized to 70 kg using equation [parameter] x [weight]/70 kg
Key: n = size of subsample; NC = Not calculated; SD = standard deviation

There was no significant difference in UGE between the 200-and 300-mg doses. Following the 200-mg dose, UGE_{24} in Indians (mean [±SD] of 37.6 [±6.79] g) was lower than what was observed in Western subjects (mean [±SD] of 56.0 [±11.1] g). The UGE rate, however, was similar in both populations.

Mean (±SD) R_T values over the first 4 hours were 60.8 (±8.90) mg/dL and 61.2 (±7.04) mg/dL for the 200- and 300-mg doses, respectively. These values were similar to what was reported previously in healthy volunteers where mean (±SD) R_T values were 68.3 (±3.0) mg/dL and 61.8 (±3.9) mg/dL following single 200-and 400-mg doses, respectively.

Mean peak plasma glucose concentrations were approximately 14% lower than baseline following a single oral administration of 200-mg JNJ-28431754 and 10% lower following the 300-mg dose. However, mean AUC_{0-4h} was unchanged following either dose. Plasma insulin concentrations and plasma C-peptide concentrations decreased following a single oral administration of JNJ-28431754 and the magnitude of the effect was similar for both the 200-and 300-mg doses. Overall, the changes in plasma glucose, insulin, and C-peptide were similar for both the 200-mg (CSR 28431754DIA1004 2009) and 300-mg doses and the effects in Indians were similar in magnitude to those observed in Western subjects.

PHARMACOGENOMIC RESULTS: Pharmacogenomic data will be pooled across comparable clinical studies with subjects of similar ethnicity.

SAFETY RESULTS:

Three subjects (20%) treated with 200 mg JNJ-28431754 experienced 4 adverse events. None of the subjects treated with 300-mg JNJ-28431754 reported any adverse event. All the adverse events were mild, except for the moderate adverse event of spontaneous abortion, which was reported as the only serious adverse event. The investigator considered the event of spontaneous abortion as doubtfully related to the study drug. There were no deaths or discontinuations due to adverse events during this study. None of the subjects had hypoglycemia during the study.

There were no clinically relevant changes in laboratory tests, vital signs, or ECG parameters.

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

CONCLUSION:

- JNJ 28431754 plasma exposure as measured by C_{max} and AUC in Indian subjects increased linearly between 200 and 300 mg.
- Body weight normalized PK parameters for Indian subjects were similar to those parameters observed in Western subjects.
- The effect of JNJ-28431754 on UGE was similar at both the 200-and 300-mg doses, but lower than previously observed in Western subjects; however the mean R_T values were similar.
- The effect of JNJ-28431754 on plasma glucose, C-peptide, and insulin were similar at both the 200-and 300-mg doses, and similar to the effects previously observed in Western subjects.
- JNJ-28431754 was safe and well tolerated following oral administration of single 200-and 300-mg tablets to Indian subjects.

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