SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Name of Finished Product	Not Applicable
Name of Active Ingredient(s)	JNJ-28431754

Protocol No.: 28431754NAP1002

Title of Study: A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single and Multiple Ascending Oral Doses of JNJ-28431754 in Type 2 Diabetes Mellitus Patients

NCT No.: NCT00963768

Clinical Registry No.: CR012451

Principal Investigator: This was a multi-center study conducted at 3 different sites. In Germany, the Principal Investigator was Sabine Arnolds, M.D., at the Profil Institut for Stoffwechselforschung GmbH, Hellerbergstrasse 9, Neuss, 41460, Germany. In San Diego, Charles Bowden, M.D. and Marcus Hompesch, M.D. were the Coordinating Investigators for the Profil, San Diego site. In Korea, the Coordinating Investigator was MinSoo Park, M.D., Director of Clinical Research Severance Hospital, Yonsei University Health System, 250 Seongsanno (134 Sinchon-dong), Seodaemun-gi, Seoul 120-752, Korea.

Publication (Reference): Data from this study has not been published.

Study Period: 08 June 2007 to 27 December 2007. Database lock date was on 26 February 2008.

Phase of Development: Phase 1

Objectives: To evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of JNJ-28431754 after single and multiple ascending oral doses of JNJ-28431754 in subjects with Type 2 diabetes mellitus (T2DM)

Methods: This was a randomized, double-blind, placebo-controlled, single and multiple (14 days) ascending dose, sequential, parallel group study. Five cohorts of subjects with type 2 diabetic mellitus (T2DM) (20 subjects per cohort) were studied. Sixteen subjects were randomly assigned to JNJ-28431754, and 4 to matching placebo within each cohort. One dose level was evaluated in each cohort. The planned doses were 30, 100, 300 and 600 mg per day. The actual doses tested in the Study were 30, 100, 200, 400 mg and 300 mg given twice daily (600 mg). An additional cohort of Korean subjects was evaluated at 30 mg, a dose tested in a prior cohort and considered to be well tolerated. After the initial screening, eligible subjects were instructed to discontinue their antidiabetic medications for 16 days, prior to dosing on Day 1. Blood glucose levels were monitored daily during the 16-day washout period to ensure that that glucose levels remained in a well tolerated range.

Eligible subjects were admitted to the Clinical Research Unit (CRU) on Day –3. On Day –2 and Day –1 all subjects received the placebo once daily in a single-blind fashion (subject blinded). Subjects were randomly assigned to a double-blind treatment with JNJ-28431754 or placebo. A single dose was administered on Day 1. Daily dosing, at approximately 8 AM every day, resumed on Day 3, and continued through Day 16. Subjects were discharged from the CRU on Day 20 (96 hours after last dosing) and returned to the CRU for safety assessments and PK sample collections on the mornings of Day 21 and Day 22. They also returned for a final follow-up visit within 7 to 10 days following the Day 22 outpatient visit. Blood and urine samples for pharmacokinetic, pharmacodynamic, and safety were collected as specified in the Time and Events Schedule, which follows the synopsis in the Study Protocol. Safety was assessed from the time of consent until the end of the study. A single blood sample (optional) was collected on Day 1 for potential genetic testing.

Number of Subjects (planned and analyzed): Of the 120 subjects planned to be enrolled, 116 subjects were randomized and dosed and 111 (96%) finished the study. All randomized subjects were included in the safety, pharmacokinetic, and pharmacodynamic analyses. Ninety-three subjects received JNJ-28431754 and 23 subjects received placebo.

Diagnosis and Main Criteria for Inclusion: Males or postmenopausal/surgically sterile females, diagnosed with T2DM for at least 12 months prior to study screening, age between 25 to 65 years, inclusive, and body mass index (BMI) between 20.0 and 39.9 kg/m^2, inclusive (BMI = $weight/height^2$). Subjects were included if their hemoglobin A1c value was 7 to 8.5% at screening and fasting plasma glucose (FPG) concentration was between 7.8 mM (140 mg/dL) and 13.3 mM (240 mg/dL) on Day –2, inclusive for subjects in the EU. For subjects in the US and Korea, they were included if their hemoglobin A1c value was 7 to 10.0% at screening, and FPG concentration was between 7.8 mM (140 mg/dL) and 15.0 mM (270 mg/dL) on Day –2, inclusive.

Test Product, Dose and Mode of Administration, Batch No.: JNJ–28431754, a white powder with very low aqueous solubility, was compounded per the dispensing procedure to obtain an oral suspension of concentration 5 or 50 mg/mL (Lot No. R14611, R14689, R14690, R14691, R14692, R14689, R14612, R14644, and R14687) in 0.5% hypromellose, and was dispensed using the provided oral dispenser.

Reference Therapy, Dose and Mode of Administration, Batch No.: A placebo for JNJ-28431754 was used as a reference. The placebo was administered orally as an aqueous solution of 0.5% weight/weight hypromellose (Methocel) (Lot No. R14613, R14645, R14688, R14693, and R14723) in a blinded manner.

Duration of Treatment: The duration of dosing with study drug was a total of 15 days with a single blind placebo dosed on Day -1 and Day -2 and double blind (treatment with JNJ-28431754 or placebo) on Days 3 to 16. Total study duration was about 8 weeks starting with screening and through the pretreatment run-in treatment period, and post study follow-up periods.

Criteria for Evaluation: Blood and urine samples for pharmacokinetic, pharmacodynamic, and safety were collected at predefined time points, as specified in the Time and Events Schedule, which follows the synopsis in the Study Protocol.

Pharmacokinetics:

On Day 1, plasma samples for concentration measurements of JNJ-28431754 and its metabolites (M7 and M5) were collected at predose and up to 48 hours postdose (total 14 samples). For cohorts with a twice-daily dosing regimen, 6 additional PK plasma samples were collected. Urine samples were collected on Day 1 at predose and up to 48 hours postdose. Plasma samples were collected at predose in the morning on Days 5, 7, 9, 11, 13, and 15 to obtain trough concentrations of JNJ-28431754 and its metabolites (M7 and M5). On Day 16, plasma samples for concentration measurements of JNJ-28431754 and its metabolites (M7 and M5) were collected at predose and up to 144 hours postdose. For cohorts with a twice daily dosing regimen, 6 additional PK plasma samples were collected. Urine samples for analysis of JNJ-28431754 were collected on Days 16 to 20 at 0 to 2 and up to 96 hours postdose.

Pharmacokinetic plasma and urine samples were analyzed for concentrations of JNJ-28431754 using selective and sensitive liquid chromatography-mass spectrometry methods under the responsibility of the Bioanalytical Group at J&JPRD. However, due to findings of inappropriate bioanalytical method and study sample analyses and the non-reconstructable nature of the analyses, bioanalytical data was not considered to be reliable and therefore concentrations of JNJ-28431754 in plasma and urine were not reported.

Pharmacokinetic plasma samples were analyzed for concentrations of M7 and M5 using validated, selective and sensitive liquid chromatography-mass spectrometry (LC-MS/MS) methods under the responsibility of the Bioanalytical Group at Johnson & Johnson, Pharmaceutical Research and Development (J&JPRD). Pharmacokinetic parameters estimated from plasma data included: C_{max}, t_{max}, t_{last}, AUC_{0-12}, AUC_{0-24h}, AUC_{∞}, λ_z, $t_{½}$, $C_{min,ss}$, $C_{max,\ ss}$, $AUC_{\tau,ss}$, AUC_{last}, FI, Acc Ratio. Pharmacokinetic parameters estimated from urinary excretion data included: Ae_{0-24} and Ae_{0-24} (% Dose).

Pharmacodynamics:

The following primary pharmacodynamic parameters were estimated at predefined time-points, as specified in the Time and Events Schedule of the Study Protocol: change from baseline (Day –1) in mean 24-hour plasma glucose (PG) concentration and change from baseline (Day –1) urine glucose excretion (UGE) with respect to cumulative amount (grams of glucose) and UGE rate (grams of glucose per hour).

The following secondary pharmacodynamic parameters were estimated at predefined time-points, as specified in the Time and Events Schedule of the Study Protocol: renal threshold (R_T); change from baseline in mean 24-hour insulin concentration; changes from baseline morning FPG and fasting plasma insulin; change from baseline PG and insulin excursions; glucose AUC_{0-2h} on Day 1, and Day 16; insulin sensitivity (S_I); two measures of beta-cell function: insulinogenic index and insulin secretion rate; plasma glucagon-like peptide-1 levels; Visual Analogue Scale (VAS) scores to assess appetite and satiety and morning fasting body weight.

Pharmacogenomic:

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

Safety:

Safety and tolerability were evaluated via an assessment of adverse events (AEs) monitored continuously throughout the study, vital signs, 12-lead ECGs, physical examinations, whole body skin assessment and clinical laboratory tests recorded as specified in the Time and Events Schedule, which follows the Synopsis in the Study Protocol. Symptomatic or asymptomatic hypoglycemia was monitored throughout the study.

Patient Reported Outcomes Evaluation:

Patient reported outcome data consisted of the questionnaire on the frequency to urinate during daytime hours, if they had an uncomfortable urge to urinate, if waking up at night due to the urge to urinate, and if they awoke due to other reasons than to urinate, collected on Days -2, 4, 7, and 14.

Statistical Methods:

Sample size: It was estimated that a sample size of 20 subjects (16 receiving active JNJ-28431754 and 4 receiving placebo) with T2DM would be sufficient to detect a 15% reduction in mean 24-hour plasma glucose with 80% power, assuming a one-sided test and a coefficient of variation of 18%.

Pharmacokinetics: Pharmacokinetic analyses of the metabolites (M7 and M5) were performed for subjects who received either 100 or 400 mg doses of JNJ-28431754. Results were summarized and descriptive statistics were generated for both the 100 and 400 mg dose levels.

Pharmacodynamics: Pharmacodynamic analyses were performed on all subjects receiving at least 1 dose of JNJ-28431754 or placebo and with at least 1 pharmacodynamic assessment. Summary statistics were generated for all pharmacodynamic assessments. Mixed effect analysis of variance modeling was used to assess the treatment effects on 24-hour mean PG and UGE (amount and rate). The estimated least squares means and appropriate 95% confidence intervals for the difference of the mean pharmacodynamic parameters were obtained for pharmacodynamic evaluations.

Safety: All the measures were summarized with descriptive statistics for each dose level and all placebo observations grouped together. All statistical analyses were considered exploratory and interpreted as such. No corrections were made for multiple comparisons.

RESULTS:

Subject Disposition: Of the 116 randomized subjects, 111 (96%) completed the study. The doses tested in the Study were 30, 100, 200, 400 mg and 300 mg given twice daily (600 mg) in Western subjects and

30 mg in Korean subjects. Two Korean subjects discontinued from the study: one subject who received placebo did not complete the study due to a serious adverse event (SAE) (cholelithiasis) and one subject who received 30 mg JNJ-28431754 discontinued the study by choice. Two subjects from the 200 mg treatment group were discontinued from the study, one for a TEAE (arrhythmia), and the other due to inappropriate behavior towards other study participants and clinic staff. One subject from the 400 mg treatment group was discontinued due to a TEAE (persistent hyperglycemia).

Demographics and Baseline Characteristics: Of the 116 subjects, 81 (70%) were male and 35 (30%) were female. In both Western and Korean subjects, the demographic and baseline characteristics are broadly comparable between the placebo and the treatment groups. However, the BMI and GFR values are lower in the Korean subjects compared with the Western subjects.

PHARMACOKINETIC, PHARMACODYNAMIC, AND PHARMACOGENOMIC RESULTS:

Pharmacokinetic results:

A subset of the total dose group population (six subjects from the 100 mg dose group and six subjects from the 400 mg dose group) were analyzed to determine M7 and M5 plasma concentrations.

Median t_{max} values were 2.5 to 3.5 hours for M7 on Day 1 and Day 16, and 4 hours for M5 on Day 1 and Day 16 for both dose groups. Mean C_{max} values for M5 and M7 on Day 1 increased by a ratio of 3.7:1 and 3.3:1, and on Day 16 increased by a ratio of 3.8:1 and 3.4:1 when dosed with 400 mg JNJ-28431754 compared to 100 mg. The corresponding mean AUC_{τ} values increased by the ratios of 3.9:1 and 3.3:1 on Day 1, and 4:1 and 3.5:1 on Day 16.

There was a mean 1.15 to 1.20-fold accumulation following multiple dosing at 100 and 400 mg for M7, suggesting no significant accumulation. Modest accumulation of M5 was evident after multiple dosing with 100 mg once daily (accumulation ratio: 1.33) and 400 mg once daily (accumulation ratio: 1.37).

Mean $t_{1/2}$ values ranged from 13.7 to 15.7 hours for metabolites M5 and M7 on Day 16. After multiple doses of 100 and 400 mg, approximately 26.3% and 22.5% of the administered dose was recovered as M7 in urine, and 11.0% and 10.7% of the administered dose was recovered as M5 in the urine in 24 hours.

Mean (SD) Pharmacokinetic Parameters for M5 and M7 on Day 1 after single dose of 100 mg or 400mg JNJ-28431754

Day 1	M7		M5	
PK Parameters	100 mg (n = 6)	400 mg (n = 6)	100 mg (n = 6)	400 mg (n = 6)
C_{max} (ng/mL)	648 (126)	2,133 (916)	322 (105)	1,188 (379)
t_{max}[a] (h)	3.50 (2.00 - 6.00)	2.50 (2.00-6.00)	4.00 (2.00-6.00)	4.00 (2.00-6.00)
AUC_{0-24} (ng.h/mL)	5,909 (1,569)	19,711 (6,309)	3,345 (1,243)	12,976 (3,891)
$t_{1/2}$ (h)	8.5 (1.4)	10.4 (1.6)	9.6 (1.1)	13.7 (2.2)

[a] Median (Range)

Mean (SD) Pharmacokinetic Parameters for M5 and M7 on Day 16 after Multiple Doses of 100 mg or 400mg JNJ-28431754

Day 16	M7		M5	
PK Parameters	100 mg (n = 6)	400 mg (n = 6)	100 mg (n = 6)	400 mg (n = 6)
C_{max} (ng/mL)	643 (191)	2,175 (640)	386 (157)	1476 (570)
t_{max}[a] (h)	3.00 (2.00 - 6.00)	2.50 (1.50 - 4.00)	4.00 (1.50 - 6.00)	4.00 (1.50 - 4.00)
AUC_{τ} (ng.h/mL)	6,717 (1,697)	23,278 (6,197)	4,471 (1,882)	17,919 (6,894)
$t_{1/2}$ (h)	13.9 (3.9)	14.9 (4.0)	13.7 (4.3)	15.7 (6.7)
Acc. Ratio[b]	1.15 (0.127)	1.20 (0.0874)	1.33 (0.124)	1.37 (0.219)
Ae_{0-24} (% Dose)	26.3 (8.17)	22.5 (2.89)	11.0 (3.81)	10.7 (4.07)

[a] Median (Range)

[b] Accu. Ratio = AUC_{τ} (Day 16) /AUC_{0-24} (Day 1)

Pharmacodynamic Results:

Urinary Glucose Excretion: At baseline on Day –1, mean 24-hour UGE in the T2DM subjects varied modestly between treatment groups with mean values ranging from 11 to 44 g at doses 30 to 400 mg once daily and 300 mg twice daily. Single 30 mg of JNJ-28431754 in Western subjects increased mean 24-hour UGE from baseline by about 64 g. No increase in the mean 24-hour UGE was observed in placebo group. As dose increased from 30 to 400 mg, the mean 24-hour UGE increased in an apparently less than dose proportional manner ranging from 60 to 150 g. The daily UGE at each dose was maintained over the 14-day dosing period. 300 mg twice daily dosing did not further increase the 24-hour UGE from that observed at 100 to 400 mg once daily doses. For the 30 mg Korean cohort, mean 24-hour UGE appeared 50% lower throughout the 2-week treatment period compared with that in the 30 mg Western subjects.

Following single dose administration on Day 1, in Western subjects, maximal UGE rate (g/h) was reached at about 4 to 6 hours postdose at all dose levels and maintained up to 9 to 12 hours. Following multiple dose administration, the maximal UGE rate generally remained constant over 24 hours at doses ≥100 mg, ranging from 4 to 7 g/h. The UGE rate at the 300 mg twice-daily dose was similar to that at the 100 to 400 mg once daily doses. Similar to the observation in the Western subjects, the UGE rate in the 30 mg Korean subjects was lower than that in the 30 mg Western subjects on Day 1 and Day 16.

Plasma Glucose Concentrations: At baseline (Day –1), FPG concentrations were comparable among treatment groups. Single doses of 30 mg, 100 mg 200 mg, and 400 mg once daily and 300 mg twice daily on Day 1, followed by a 48 hour safety monitoring period (no dosing on Day 2), and then once daily dosing for 14 days (Day 3 to Day 16) reduced mean 24-hour PG and FPG concentrations dose dependently. See the table below.

Mean (SD) and Statistical Analysis of Mean 24 Hour Plasma Glucose Concentrations (mg/dL) at Each Treatment in Study 28431754-NAP-1002
Pharmacodynamic Analysis Set

Dose	Placebo	Placebo (Korean)	30 mg	30 mg (Korean)	100 mg	200 mg	400 mg	300 mg b.i.d.
	N=19	N=4	N=16	N=15	N=16	N=16	N=16	N=14
Day -1	223 (51.0)	261 (65.2)	223 (33.9)	238 (35.1)	212 (40.9)	221 (51.6)	242 (69.7)	206 (51.6)
Day 1	219 (50.0)	261 (66.7)	203 (27.9)	221 (35.0)	185 (27.5)	188 (33.0)	196 (44.3)	168 (30.3)
Day 16	205 (40.9)	210 (76.4)[b]	200 (36.6)	182 (29.2)[a]	165 (26.4)	168 (24.5)[a]	167 (27.8)[c]	151 (23.8)
Day 1 - Day -1	-3.60 (12.1)	0.0721 (5.32)	- 19.7 (11.3)	-16.7 (9.57)	- 27.1 (17.1)	- 33.2 (24.6)	- 46.2 (28.6)	-38.4 (24.4)
Day 1 % change from Day -1	-1.49%	-0.0176%	- 8.55%	-7.04%	- 12.0%	-13.9%	-17.8%	-17.2%
95% CI & p-value vs Placebo	NA	NA	(-11.1%, -3.1%) 0.001	(-13.7%, -.4%) 0.038	(-14.5%, -6.5%) <.0001	(-16.4%, -8.4%) <.0001	(-20.3%, -12.3%) <.0001	(-19.9%, -11.6%) <.0001
Day 16 - Day -1	- 18.0 (25.7)	-62.5 (16.4)[b]	- 22.3 (18.8)	-59.5 (18.4)[a]	- 47.6 (24.7)	- 56.8 (42.6) [a]	- 64.2 (36.9) [c]	-54.8 (30.6)
Day 16 % change from Day -1	- 6.99%	-23.9[b] %	- 10.0%	-24.6[a] %	- 21.6%	- 23.1[a] %	- 26.3%[c]	-24.9%
95% CI & p-value vs Placebo	NA	NA	(-9.5%, 3.4%) 0.353	(-12.8%, 12%) 0.92	(-21.1%, -8.1%) <.0001	(-22.9%, -9.4%) <.0001	(-25.9%, -12.7%) <.0001	(-24.6%, -11.1%) <.0001

[a] n = 14
[b] n = 3
[c] n = 15

Mean (SD) and Statistical Analysis of Fasting Plasma Glucose Concentrations (mg/dL) at Each Treatment in Study 28431754-NAP-1002
Pharmacodynamic Analysis Set

Dose	Placebo	Placebo (Korean)	30 mg	30 mg (Korean)	100 mg	200 mg	400 mg	300 mg b.i.d.
	N=19	N=4	N=16	N=15	N=16	N=16	N=16	N=14
Day -1	210 (42.5)	205 (43.8)	199 (29.9)	191 (28.2)	205 (35.3)	208 (49.7)	208 (53.4)	199 (44.9)
Day 16	184 (35.1)	158 (19.7)[b]	179 (26.6)	141 (25.4)[a]	151 (28.3)	143 (18.8)[a]	141 (20.6)[c]	133 (24.8)
Day 16 - Day -1	- 25.3 (35.6)	-60.5 (24.7)[b]	- 20.8 (22.3)	-52.8 (22.8)[a]	- 53.8 (23.1)	- 65.2 (52.0) [a]	-60.2 (47.9) [c]	-66.3 (35.1)
Day 16 % of Day -1	- 10.7%	-26.9 % [b]	- 9.73%	-27.0 % [a]	- 25.8%	- 28.0 % [a]	-27.2%[c]	-31.8%
95% CI & p-value vs Placebo	NA	NA	(-8.1%, 10.1%) 0.82	(-17%, 16.9%) 0.99	(-24.1%, -6%) 0.001	(-26.7%, -7.9%) 0.0004	(-25.7%, -7.3%) 0.001	(-30.5%, -11.7%) <.0001

[a] n = 14
[b] n = 3
[c] n = 15

Plasma Insulin Concentrations: After 2 weeks of the treatment, mean percent changes from baseline (Day -1) in mean 24-hour plasma insulin concentrations were –5.08%, -22.2%, -25.7%, –23.8% and -30.0% for the 30 mg, 100 mg, 200 mg, and 400 mg once daily and 300 mg twice daily dose groups, respectively. In contrast, placebo treatment for 2 weeks resulted in 1.39% increase in mean 24-hour plasma insulin concentration. The reduction in plasma insulin levels upon JNJ-28431754 treatment was consistent with the markedly reduced PG concentrations associated with increased UGE. In Korean subjects, 30 mg JNJ-28431754 produced similar effect on mean 24-hour insulin concentrations relative to the placebo treatment.

Renal Threshold for Glucose Excretion (R_T): Renal glucose reabsorption capacity in subjects with type 2 diabetes increased with increasing plasma glucose concentrations. All treatment groups lowered R_T by more than 100 mg/dl when compared to the baseline.

Insulin Sensitivity: There were apparent increases in S_I on Day 16 at the 400 mg once daily and the 300 mg twice-daily doses of JNJ-28431754. Despite achieving considerable glucose lowering, no statistically significant increases in S_I were observed at 100 mg and 200 mg doses.

Insulin Secretion Rate: Insulin Secretion Rate (ISR) calculated at 8, 10, and 12 mM glucose concentrations was increased by greater than 50% after 2 week treatment with JNJ-28431754 compared to the baseline (Day –1) for 100 mg and higher doses, suggesting that, in addition to directly lowering PG concentrations by increasing UGE as a result of sodium glucose co-transporter 2 inhibition by JNJ-28431754, treatment for 2 weeks appeared to improve the beta cell function.

Body Weight: A progressive, dose dependent reduction in body weight from baseline (Day –1) to Day 16 was observed over the 2 weeks of treatment with JNJ-28431754. At 100 mg and higher doses, mean body weight decreased by about 1 to 1.5 kg more than the weight reduction in the placebo group. Treatment with the 30 mg dose in both Western and Korean subjects reduced body weight, but to an extent comparable to placebo. There was no apparent relationship observed between individual body weight change from baseline and the 24-hour urine volume change from baseline, suggesting that the observed weight loss might be attributable, in part, to the calories lost as glucose in urine.

Assessment of Appetite and Satiety Using Visual Analogue Scale: There were no statistically significant differences observed in any change from baseline visual analogue scale (VAS) scores at all (except 300 mg twice daily) dose levels compared with the placebo. The subjects receiving 300 mg twice daily reported feeling more hungry compared to placebo. These subjects, consistent with their hunger score, also reported increase in prospective food consumption scores compared to placebo treated subjects.

Patient Reported Outcomes Evaluation:

There were no apparent differences in the patient reported outcome data between the placebo and doses of JNJ-28431754 at 30, 100, 200, and 400 mg administered once daily, 300 mg administered twice daily in Western subjects and 30 mg administered once daily in Korean subjects.

PHARMACOGENOMIC RESULTS: There were no pharmacogenomic analyses performed in this study.

SAFETY RESULTS:

There were no deaths during this study. Two SAEs were reported in the Korean cohort. One subject who received 30 mg of JNJ-28431754 was hospitalized for acute enterocolitis 11 days after the last dosing with a recent history of ingesting raw oysters. One subject who received placebo was hospitalized for severe abdominal pain on Day 14 associated with multiple gallbladder stones. Both SAEs were considered by the Korean Investigator to be not related to the study drug and were resolved with incident. Two subjects discontinued from the study due to TEAEs. Once subject receiving 200 mg of JNJ-28431754 was discontinued from the study on Day 2 due to asymptomatic, transient ventricular arrhythmia post dose on Days 1 and predose on Day 2. One subject who received 400 mg of JNJ-28431754 was discontinued from the study on Day 7 due to persistent hyperglycemia.

For Western subjects, 17 (89%) of 19 subjects treated with placebo and 63 (81%) of 78 subjects treated with JNJ-28431754 reported treatment emergent adverse events (TEAEs). For Korean subjects, 4 (100%) of 4 subjects treated with placebo and 12 (80%) of 15 subjects treated with JNJ-28431754 reported TEAEs.

The majority of the TEAEs were mild to moderate in intensity. The majority of the TEAEs were considered not related, doubtfully related or possibly related to the study drug. None of the TEAEs were considered probably or very likely related to the study drug.

The most frequent TEAE were ECG application site reactions and skin erythema. The incidence of the skin TEAEs was not dose dependent. These skin TEAEs were transient, and resolved from within a few hours to a few days. In subjects with skin TEAEs, there were no associated constitutional or systemic abnormalities observed in routine clinical or laboratory safety evaluations. For Western subjects, 10 skin TEAEs (1 at placebo dose: erythema; 3 at 30 mg dose: lichenification, generalized pruritus and psoriasis; 5 at 100 mg dose: 4 erythema and 1 pruritus and 1 at the 400 mg dose: skin irritation, were considered by the investigator as possibly related to the study drug. Majority of the skin TEAEs were mild in severity. There were 4 moderate skin TEAEs (2 at placebo dose: erythema, rash popular; 2 at 100 mg dose: erythema, pruritius). One subject who received 30 mg dose developed moderate to severe generalized pruritus on Day 2, which was not accompanied by other skin findings and lasted about 2 days. For Korean subjects, the skin TEAEs in subjects who received 30 mg JNJ-28431754 were folliculitis in 1 subject, eczema in 2 subjects, erythema in 2 subjects, urticaria in 1 subject, furuncle in 3 subjects and erythematous rash in 2 subjects. One Korean subject who received placebo reported skin lesion, hordeolum, furuncle and a scratch mark. All skin TEAEs were mild in severity and were considered by the investigator not related to be or doubtfully related to the administration of study drug.

Clinical Laboratory Tests: No symptomatic or asymptomatic hypoglycemia was observed during the treatment period at any dose level. Two subjects at the 30 mg dose level, each reported a transient, mild episode of hypoglycemia after the treatment period (one subject reported hypoglycemia on Day 22, and the other on Day 28). Both subjects had resumed their pre-study anti-diabetic medications on Day 22 and had been discharged from the study center on Day 20. No hypoglycemia was observed during the treatment period at any dose level. No hypoglycemia was observed during both treatment and posttreatment periods in Korean subjects treated with 30 mg JNJ-28431754.

No clinically significant changes during the treatment period were observed in serum osmolality and electrolyte levels. Mean serum magnesium concentrations increased from baseline values, on average, by about 15% to 20% at the 400 mg dose. This increase was apparent as early as 24 hours after the first JNJ-28431754 dose, persisted variably over the 2-week-dosing period, and declined toward baseline after the last dose. Mean serum phosphate concentrations also increased from baseline at the 400 mg once daily and 300 mg twice-daily doses by about 14% to 30%. This increase in serum phosphate level occurred as early as 24 hours after the first JNJ-28431754 dose, but declined back to baseline levels over the next 2 weeks as dosing continued.

For Western subjects, no clinically significant changes during the treatment period were observed in routine hematology and urine laboratory tests. Although values for some parameters for some subjects were occasionally slightly outside the normal range for all treatment groups, these changes were transient and were not considered clinically significant. For the 30 mg Korean cohort, mild decreases in hemoglobin, white blood cells and lymphocytes were reported in 1 (25%) of 4 subjects who received placebo and 5 (33%) of 15 subjects who received JNJ-28431754. The Principal Investigator considered these decreases in the hematological parameters in these subjects not related to the study drug, but possibly related to the volume of blood drawn (~500 mL) for safety, pharmacokinetic, and pharmacodynamic assessments during the study.

Urine Volumes, Fluid Intake, and Urine Electrolytes: At baseline (Day –1), mean 24-hour urine volume was on average approximately 2 to 4 liters in all treatment groups. There was no persistent increase from baseline in daily 24-hour total urine volumes over the dose range studied, despite significantly elevated 24-hour UGE. Total daily fluid intake (including meal-related fluids) generally matched the total daily urine volumes. There were no persistent changes in urinary excretion of measured electrolytes after 2-weeks of treatment with JNJ-28431754. Urinary fractional excretion of uric acid appeared to increase by 30 to 100% at doses ≥100 mg over the two weeks of treatment period compared to the Day –1 level. The increased urinary excretion of uric acid was accompanied by about 20% decrease in serum uric acid level. These changes in urine and serum uric acid were not observed in subjects who received placebo. There

were no persistent changes in urinary excretion of electrolytes after 2-weeks of treatment in Korean subjects treated with 30 mg JNJ-28431754 as compared with subjects treated with placebo.

Renal Function: Total 24-hour urine N-acetyl-beta-D-glucosaminidase (NAG) activity, beta-2-microglobulin, and albumin excretion, and creatinine clearance were closely monitored in this study. On Day 1, mean 24-hour urine NAG activity increased from baseline (Day –1) in all JNJ-28431754 dose groups, but not in the placebo group. For Western subjects, mean percent increases from baseline in 24-hour urine NAG activity on Days 1 and 16 were about 0.1% and -15%, 45% and 22%, 47% and 66%, 98% and 80%, 55% and 105%, and 57% and 55% for the placebo, 30 mg, 100 mg, 200 mg and 400 mg once daily, and 300 mg twice daily dose groups, respectively. For the 30 mg Korean cohort, the increase in the 24-hour NAG activity started on Day 6 and persisted over the remainder of the 2 week treatment period. Mean percent increases from baseline in 24-hour urine NAG activity on Days 6 and 16 were –12% and –43%, and 18% and 36%, for the placebo and subjects treated with JNJ-28431754, respectively. The increases in the 24-hour urine NAG activity persisted up to 72 hours post the last dose. 24-hour urine NAG activity was not determined at the follow-up visit. For Western subjects, mean percent increases from baseline in 24-hour urine β-2-microglobulin were about 12% and -0.2%, 8% and -2%, 9% and -11%, 28% and 0.9%, 21% and 8%, and 37% and 9% for the placebo, 30, 100, 200, and 400 mg once daily, and 300 mg twice daily dose groups on Day 1 and 16, respectively. For the 30 mg Korean cohort, mild increase from baseline in 24-hour β-2-microglobulin was observed on Day 16. Mean percent increases from baseline in 24-hour urine β-2-microglobulin were 6% and 29% on Day 16 for the placebo and JNJ-28431754 cohorts, respectively. This increase in β-2-microglobulin appeared to decrease to baseline level post the last dose. Increases in urine osmolality were observed at all JNJ-28431754 treated groups throughout the 2-week dosing period. Mean percent increases in 24-hour urine osmolality ranged from 30% to 80% and was not dose-dependent.

No clinically meaningful changes in daily 24-hour urine albumin or 24-hour creatinine clearance were observed after 2 weeks of treatment with JNJ-28431754. Mean serum creatinine levels increased over the 2 weeks of treatment by about 20% compared to Day –1 at doses ≥200 mg. These increases persisted variably or tended to decrease during the 2-week treatment period. On Day 17 (24 hours after the last dose), mean percent changes from baseline in serum creatinine levels are 6%, 6%, 5%, 14%, 10% and 12% for the placebo, 30 mg, 100 mg, 200 mg, 400 mg once daily and 300 mg twice-daily doses, respectively. By Day 22 (5 days after the last dose), mean serum creatinine levels at all JNJ-28431754 dose groups were comparable to that in the placebo group. A similar trend was observed for the serum BUN levels.

Bone Markers: There were no treatment-related changes in serum osteocalcin, serum bone-specific alkaline phosphatase, serum parathyroid hormone, urine deoxypyridinolines and urine N-telopeptides. There were decreases in serum 1,25-dihydroxy Vitamin D levels in JNJ-28431754 treated groups as compared with the placebo treated group. The decrease, from predose (about -30%) in serum 1,25-dihydroxy Vitamin D level, was observed on Day 5 at doses ≥200 mg. On Day 17 (24 hours after the last dose), the percent decreases from baseline in mean serum 1,25-dihydroxy Vitamin D levels were -2%, 6%, -12% and -11% for the placebo, 200 mg, 400 mg once daily and 300 mg twice daily dose groups, respectively. The decreased serum 1,25-dihydroxy Vitamin D level returned towards the baseline level after the last dose of JNJ-28431754.

Vital Signs and ECGs: Supine blood pressure (BP), especially systolic BP, appeared to be reduced after 2 weeks of treatment with JNJ-28431754. In Western subjects, mean changes in systolic BP from baseline (mean of predose values) on Day 16 ranged from –5 to –11 mmHg at all JNJ-28431754 doses studied. For the placebo treated subjects, mean change in systolic BP from baseline was –3 mmHg. In Korean subjects, mean changes in systolic BP from baseline on Day 16 were 1 and –2.5 mmHg for the placebo and 30 mg JNJ-28431754 groups, respectively. The decreased BP was not associated with increase in supine pulse rate.

There were no apparent dose-related or treatment-related trends in ECG parameters observed during the study. There were a few subjects who had increases in change from baseline QTcF and QTcB intervals between 30 and 60 msec, but these changes were not dose dependant and were deemed by the investigator not to be clinically significant. No subject experienced an increase in QTcF or QTcB interval greater than 60 msec from baseline.

STUDY LIMITATIONS:

The number of Korean subjects who were treated with JNJ-28431754 (N=15) and placebo (N=4) was not balanced. Therefore, the data in Korean subjects is limited in comparison between the treated and the placebo subjects.

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