# 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.:** 28431754NAP1004

**Title of Study:** An Open-Label, Fixed Sequence, Single and Multiple Dose Study in Male and Female Subjects to Investigate the Potential for Pharmacokinetic and Pharmacodynamic Interaction Between Metformin and JNJ-28431754

**Principal Investigator:** Magdy L. Shenouda, M.D. MDS Pharma Services, [redacted], USA

**Publication (Reference):** None

**Study Period:** First subject screened was on 11 October 2007. The last subject follow up was on 19 November 2007. The database was locked on 28 November 2007.

**Phase of Development:** Phase 1

**Objectives:**

Primary:

- To compare the pharmacokinetics of JNJ-28431754 (maximum serum concentration [$C_{max}$] and area under the curve [AUC]) following multiple once-daily dosing with 100 mg JNJ-28431754 when dosed alone or together with a single 1,000 mg dose of metformin in healthy male and female subjects.
- To compare the pharmacokinetics of metformin ($C_{max}$ and AUC) following a single 1,000 mg dose of metformin when dosed alone or together with a 100-mg dose of JNJ-28431754 following multiple once-daily dosing with JNJ-28431754, in healthy male and female subjects.
- To compare the pharmacodynamics of JNJ-28431754 (24-hour urine glucose excretion [$UGE_{24h}$] and 24-hour serum glucose AUC [glucose $AUC_{24h}$]) when dosed alone following multiple once-daily dosing with 100 mg JNJ-28431754 or together with a single 1,000 mg dose of metformin in healthy male and female subjects.

Secondary:

- To evaluate the safety and tolerability of multiple doses of 100 mg JNJ-28431754 when administered alone and in combination with a single 1,000-mg dose of metformin in healthy male and female subjects.

**Methods:**

- This study was an open-label, fixed sequence, single and multiple dose study in male and female subjects to evaluate the potential for pharmacokinetic and pharmacodynamic interaction between JNJ-28431754 and metformin. The safety and tolerability of JNJ-28431754 and metformin when dosed together, and alone, were also evaluated.
- Eighteen healthy male and postmenopausal or surgically sterilized female subjects were enrolled and received a single oral dose of 1,000 mg metformin on Day 1, once-daily dosing with 100 mg JNJ-28431754 on Days 4 to 7 and a single oral dose of 1,000 mg metformin co-administered with 100 mg JNJ-28431754 on Day 8.

- After providing written informed consent, subjects were screened within 21 days before Day 1. Eligible subjects were then admitted to the clinical research unit (CRU) on Day -2 and underwent clinical laboratory assessments as well as testing for urine alcohol, drugs of abuse, cotinine, and for pregnancy. Baseline safety and pharmacodynamic assessments were done on Day -1. Subjects were discharged from the CRU on Day 11, 72 hours post last dose on Day 8. All subjects returned to the CRU for a follow-up visit 7 to 10 days after final dose of study drug (Day 15 to 18).

**Number of Subjects (planned and analyzed):** A total of 18 subjects were planned and analyzed for safety and pharmacokinetics in this study.

**Diagnosis and Main Criteria for Inclusion:** Subjects included in the study were healthy males and females of non-child bearing potential between 18 and 55 years of age, inclusive; body mass index (BMI) between 18.5 and 35 kg/m² (inclusive); without a history of chronic intake of acetylsalicylic acid greater than 100 mg/day, other non steroidal anti inflammatory drugs, anticoagulants or other drugs known to interfere with blood clotting within 3 months of study start, or anticipated a need to take any of these during the course of the study; and without a history of cutaneous hypersensitivity to sunlight or artificial source of intense light, especially ultraviolet light.

**Test Product, Dose and Mode of Administration, Batch No.:** The study medications consisted of 25 mg of JNJ-28431754 tablets (Lot No. 07069/R14698) and 1,000 mg of metformin HCl, Lot# HL8957 (sourced by the contracting facility from Bayshore Pharmacy, [redacted] USA) immediate release tablets. The study medications were stored protected from the white light.

**Reference Therapy, Dose and Mode of Administration, Batch No.:** Not applicable for this study.

**Duration of Treatment:** The duration of the study drug therapy was 8 days. The entire duration of the study, from screening until final follow-up visit was approximately 39 days, of which the subjects resided in the CRU for 13 days.

**Criteria for Evaluation:**

Pharmacokinetic Evaluations: Serum samples were planned to be analyzed to determine concentrations of metformin and JNJ-28431754 using a validated, specific and sensitive LC-MS/MS method, under the supervision of the Sponsor's Bioanalytical Laboratory Department of Bioanalysis. Pharmacokinetic parameters estimated from serum data included: $C_{max}$, $t_{max}$, $t_{1/2,\lambda}$, $AUC_{last}$, $AUC_{\infty}$ and $\lambda_z$ for metformin, and $C_{max,ss}$, $t_{max}$, and $AUC_{24h}$ for JNJ-28431754

Pharmacodynamic Evaluations: The key pharmacodynamic evaluation in this study was to compare whether the $UGE_{0-24hr}$ on Day 7 (JNJ-28431754 dosed alone) differs in relation to the $UGE_{0-24h}$ on Day 8 (JNJ-28431754 dosed together with metformin). Baseline UGE was determined on Day -1. A similar comparison was made for serum glucose and insulin $AUC_{0-16h}$.

Safety Evaluations: Safety was evaluated by examining the incidence and type of treatment emergent adverse events (TEAE), and changes in clinical laboratory test values (blood chemistry, hematology, and urinalysis), physical examination results, skin assessment, 12-lead ECGs, and vital sign measurements from screening through to study completion. Safety evaluations also included serology testing (hepatitis B surface antigen, hepatitis C antibodies, and human immunodeficiency virus [HIV] antibodies), and urine alcohol, cotinine, and drugs of abuse screening. The use of concomitant medication was recorded throughout the study.

Pharmacogenomics: A blood sample (10 mL) was collected on Day 1, from subjects who gave consent to allow for pharmacogenomic research, as necessary.

**Statistical Methods:**

The sample size was calculated based on published variability estimates on AUC and $C_{max}$ for metformin. It was estimated that a sample size of 18 subjects would provide more than 80% power to detect a 30% difference in AUC between metformin alone and metformin administered with

JNJ-28431754 based on log-scale with a two-sided alpha of 0.05. Also, if the expected ratio of geometric means of metformin administered with JNJ-28431754 to metformin alone was 1, the sample size of 18 would provide estimated 95% confidence interval of (0.799, 1.25).

The effect of JNJ-28431754 on pharmacokinetics of metformin and vice versa was assessed using mixed effects linear models. The statistical analyses of AUC and $C_{max}$ were planned to be performed based on log-transformed data. The estimated least square means and 90% confidence intervals (CI) for the differences were back transformed to provide ratios of AUC and $C_{max}$ for the metformin administered alone versus metformin administered with JNJ-28431754. Similar analyses were planned to be performed to compare AUC and $C_{max}$ for JNJ-28431754 administered alone versus when administered with metformin. JNJ-28431754 pharmacokinetic results were planned to be compared on Days 7 and 8.

The effect of metformin on the pharmacodynamics of JNJ-28431754 was assessed using mixed effects linear models. The statistical analyses of 24-hour urine glucose excretion ($UGE_{24h}$) and 16 hour serum glucose AUC (glucose $AUC_{16h}$) were performed by fitting appropriate linear models. The estimated least square means and 90% CI for the differences were provided for $UGE_{24h}$ and glucose $AUC_{16h}$ to compare JNJ-28431754 administered alone versus when administered with metformin.

**RESULTS:**

Fifteen (83%) of the 18 randomized subjects completed the study. Three (17%) subjects did not complete the study; 2 subjects discontinued due to their own choice and 1 subject was withdrawn by the Principal Investigator (PI) due to difficulty in obtaining blood samples.

DEMOGRAPHICS AND BASELINE CHARACTERISTICS:

Normal healthy subjects were enrolled for the study of which 11 (61%) subjects were black, 5 (28%) subjects were white, 1 (6%) subject was White/Hispanic or Latino and 1 (6%) subject was Asian. Seventeen (94%) males and 1 (6%) female were enrolled in this study. The enrolled subjects were between 25 and 54 years of age and the BMI ranged from 20.3 $kg/m^2$ to 33.9 $kg/m^2$ (mean 28.21 $kg/m^2$).

PHARMACOKINETIC RESULTS:

The effect of metformin on the pharmacokinetics of JNJ-28431754: No pharmacokinetic parameters of JNJ-28431754 were estimated due to inappropriate bioanalytical analysis, thus the effect of metformin on JNJ-28431754 could not be evaluated.

The effect of JNJ-28431754 on the pharmacokinetics of metformin: Systemic exposure (AUC) of metformin was similar when administered alone or in combination with JNJ-28431754. Geometric mean $C_{max}$ of metformin decreased 14% when metformin was administered in combination with JNJ-28431754 compared to metformin administration alone. The 90% CIs for the geometric mean ratios for AUC associated with metformin were within the 0.80 to 1.25 boundaries. However, 90% CIs for the geometric mean ratios for $C_{max}$ associated with metformin were outside the lower limit of these boundaries.

Statistical Analysis of Metformin Pharmacokinetic Parameters Following Single Dose Administration of 1,000 mg Metformin With and Without 100 mg of JNJ-28431754
Study 28431754-NAP-1004
(Pharmacokinetic Analysis Set)

| Pharmacokinetic Parameter | Metformin alone Geometric LS Mean Day 1 | Metformin with JNJ-28431754 Geometric LS Mean Day 8 | Ratio of Geometric means | 90% CI |
|---|---|---|---|---|
| $AUC_{\infty}$ (ng.hr/mL) | 8,362 | 8,071 | 0.965 | 0.819 - 1.137 |
| $C_{max}$ (ng/mL) | 1,104 | 945.5 | 0.856 | 0.729 - 1.007 |

LS mean = least-squares mean, CI = confidence interval

The amount excreted (Ae) in urine for metformin was comparable after dosing with both regimens (metformin alone: 279 mg [27.9%]; metformin + JNJ-28431754: 265 mg [26.5%]). Overall, JNJ-28431754 had no meaningful effect on the pharmacokinetics of metformin.

PHARMACODYNAMIC RESULTS:

Urine Glucose Excretion: Following metformin administration on Day 1, approximately 0.121 grams (g) of glucose was excreted in urine over a 24-hour period. The $UGE_{24h}$ following repeated dosing with 100 mg JNJ-28431754 on Day 7 (48.0 g/24 hours) was not altered upon co-administration with a single 1,000 mg dose of metformin on Day 8 (47.0 g/24 hours). Therefore, co-administration of metformin on Day 8 did not cause any significant change in $UGE_{24h}$.

Serum Glucose: The ratio of geometric means and 90% CIs for serum glucose $AUC_{0-16h}$ values for metformin showed that co-administration of JNJ-28431754 with metformin had no significant effect on serum glucose $AUC_{0-16h}$ compared to that of metformin alone. Similarly following co-administration of JNJ-28431754 with metformin, there was no significant effect on serum glucose $AUC_{0-16h}$ ($p = 0.49$) compared to that of JNJ-28431754 alone.

Serum Insulin: The ratio of geometric means and 90% CIs for serum insulin $AUC_{0-16h}$ values showed that co-administration of metformin with JNJ-28431754 had no significant effect on serum insulin $AUC_{0-16h}$ ($p = 0.21$) compared to that of metformin alone. Similarly following co-administration of JNJ-28431754 with metformin, there was no significant effect on serum insulin $AUC_{0-16h}$ ($p = 0.40$) compared to that of JNJ-28431754 alone.

SAFETY RESULTS:

All subjects were to receive metformin alone (Day 1), JNJ-28431754 alone (Days 4 to 7), and JNJ-28431754 with metformin (Day 8). Following metformin alone, 2 (11%) subjects had treatment emergent adverse events (TEAEs). Seven (41%) subjects that received 100 mg of JNJ-28431754 alone, experienced TEAEs and when both drugs were given together, 2 (13%) of 16 subjects experienced TEAEs. The most common TEAEs were gastrointestinal disorders with 5 (28%) of 18 subjects reporting diarrhea, flatulence, or constipation. All of the TEAEs were of mild severity except 2, which were considered to be of moderate severity (Subject [redacted] with constipation and Subject [redacted] with euphoria).

Two [redacted] subjects, one [redacted] years of age (Subject [redacted] and the other [redacted] years of age (Subject [redacted] each reported a sense of euphoria, after receiving 100 mg dose of JNJ-28431754. The PI listed both as being possibly related to JNJ-28431754. Two [redacted] subjects, one [redacted] years of age (Subject [redacted] and the other [redacted] years of age (Subject [redacted] following 100 mg JNJ-28431754 experienced mild skin rashes that were considered possibly related to JNJ-28431754 by the Principal Investigator (PI). Both were given topical 1% hydrocortisone after which the rashes resolved. Two [redacted] subjects, one [redacted] years of age (Subject [redacted] and the other [redacted] years of age (Subject [redacted] following 100 mg JNJ-28431754 plus 1,000 mg metformin, experienced diarrhea. The PI listed both as being probably

related to the study drugs. Subject [redacted] a [redacted] receiving 100 mg JNJ-28431754 experienced mild flatulence, which was considered by the PI to be possibly related to JNJ-28431754.

There were no deaths, serious or severe adverse events in this study. There were no TEAEs leading to discontinuation. No hypoglycemia was observed within any study sequence. There was no apparent relationship between study medications and the type, severity or incidence of TEAEs.

No clinically significant, treatment-emergent, abnormal changes were observed in hematology, serum electrolytes and other clinical chemistry tests, routine urine analyses and serology. Although values for some parameters were slightly outside the normal range at isolated time points in some subjects, these changes were transient and were not considered clinically significant.

There were no indications of any consistent treatment-related effect on any of the vital signs or changes in any of the ECG parameters, following oral administration of multiple doses of JNJ-28431754 100 mg with or without metformin in healthy subjects.

STUDY LIMITATIONS:

The data from this study suggests a lack of pharmacokinetic and/or pharmacodynamic interaction between JNJ-28431754 and metformin. However, since this study was performed in healthy subjects with a 100 mg dose of JNJ-28431754 and a single 1,000 mg dose of metformin, the apparent lack of any pharmacokinetic and/or pharmacodynamic interaction between JNJ-28431754 and metformin will need to be confirmed in type 2 diabetic subjects at the therapeutic dose of JNJ-28431754 and with multiple dosing of metformin at a therapeutic dose.

CONCLUSION:

- JNJ-28431754 100 mg was well tolerated in healthy normal subjects when given in multiple doses alone (100 mg/day for 4 days) and when co-administered with a single 1,000 mg dose of metformin.
- Concomitant administration of JNJ-28431754 with metformin did not affect the AUC but marginally decreased the mean $C_{max}$ of metformin by 15%. These results suggest that JNJ-28431754 has no clinically significant effect on serum concentrations of metformin.
- The $UGE_{24h}$ following repeated dosing with JNJ-28431754 was not altered upon co-administration with a single dose of metformin.
- Co-administration of a single dose of metformin with JNJ-28431754 had no significant effect on the mean serum glucose AUC and insulin AUC in healthy subjects compared to each treatment alone (metformin or JNJ-28431754).

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