SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development
Name of Finished Product	To be determined
Name of Active Ingredient	JNJ-28431754

Protocol No.: 28431754NAP1006

Title of Study: An Open-Label Study to Investigate the Absorption, Metabolism, and Excretion of JNJ-28431754 in Healthy Male Subjects Following a Single Oral Dose Administration of ^{14}C-JNJ-28431754

EudraCT Number: 2007-004218-15

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

Study Period: First subject admitted to clinic for baseline measurements was on 05 September 2007 with the last follow-up visit on 04 October 2007. The database was locked on 19 October 2007.

Phase of Development: Phase 1

Objectives:

- Primary Objective: To investigate the absorption, metabolism, and excretion of JNJ-28431754 in healthy adult men after a single 196 mg oral dose of ^{14}C-JNJ-28431754
- Secondary Objective: To assess the safety and tolerability of a single 196 mg oral dose of JNJ-28431754 in healthy subjects

Methods:

- This was a single-dose, single-center, open-label study in healthy adult males to characterize the routes of excretion of JNJ-28431754 and to elucidate its metabolic pathways and structures of its predominant metabolites.
- Potential subjects were screened within 21 days prior to dosing. Eligible subjects were admitted to the clinical unit on Day −1. Subjects resided in the study unit from Day −1 to Day 8.
- Six subjects received a single oral dose of ^{14}C-JNJ-28431754 on Day 1 after an overnight fast of at least 8 hours.
- Radioactivity in blood, plasma, urine, and feces was measured. Qualitative (structure identification) and quantitative metabolite profiling of JNJ-28431754 in plasma, urine, and feces was performed. Total radioactivity (TR) excreted in urine and stool collections was closely monitored for up to 168 hours postdose (Days 1 to 8) to determine whether the subject could be discharged on Day 8.
- On Day 8, subjects who did not show slow excretion of the radiolabel dose, ie, none of their 120 to 144 hours postdose (Days 6 to 7) and 144 to 168 hours postdose (Days 7 to 8) collections of urine and stool samples accounted for ≥ 2% of the administered dose per 24 hours, were discharged from the study unit after completing the discharge procedures. Subjects if, by Day 8, had slow excretion of the radiolabel dose, resided in the study unit up to Day 14.
- Subjects discharged on Day 8 returned for final safety follow up between Day 10 and Day 14. Subjects discharged after Day 8 returned for follow up between Day 17 and Day 21.

- Subjects' safety and tolerability was monitored throughout the study. A pharmacogenomic research blood sample was collected on Day 1, from subjects who consented separately to the pharmacogenomic component of the study. Number of Subjects (planned and analyzed): Six subjects were enrolled and completed the study.

Diagnosis and Main Criteria for Inclusion: Healthy non-smoking male subjects, between 18 and 45 years of age (inclusive); with a body mass index (BMI) between 18 and 30 kg/m^2 (inclusive) and a body weight of not less than 50 kg were enrolled in this study.

Test Product, Dose, and Mode of Administration, Batch No.: ^{14}C-JNJ-28431754, specifically labeled with ^{14}C on the benzylic carbon between the methylphenyl and the thiophene ring systems, was supplied as 48.5 mg/mL liquid suspension in 0.5% hypromellose (Methocel®) with specific radioactivity of 7.6 kBq/mg.

On the day before dosing, ie, 5 days after preparation of the formulation the radioactivity concentration was 364.2 kBq/mL and the radiochemical purity was 99.8%. The average JNJ-28431754 dose dispensed per unit (4 mL) was 192 mg of the hemihydrate, comprising a radioactivity dose of 1,451 kBq or 39.2 μCi. The actual dose of the base form of JNJ-28431754 was 188 mg. This was not the planned 196 mg dose of the base form of JNJ-28431754. Nevertheless, this did not impact or change any study findings.

Each subject in the study swallowed 4 mL, representing a 188 mg dose and an amount of radioactivity equal to amount of 1,451 kBq (39.2 μCi). The batch number for ^{14}C-JNJ-28431754 was 2161.

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

Duration of Treatment: The total study duration was approximately 5 weeks (including screening and safety follow-up).

Criteria for Evaluation:

Pharmacokinetic Evaluation:

Venous blood, urine, and fecal samples were collected for up to 168 hours postdose. Total radioactivity of ^{14}C was measured in blood, plasma, urine, and feces. Metabolite profiling that includes qualitative (structure identification) and quantitative identification was performed in plasma, urine, and feces.

Plasma and urine samples were analyzed for JNJ-28431754 concentrations by using a specific and sensitive liquid chromatography tandem mass spectrometry method. However, both the human plasma/urine method validation and study sample analysis for JNJ-28431754 were determined to be not validated in this study, and therefore the pharmacokinetic data analysis for JNJ-28431754 was not considered to be acceptable and not reported. Pharmacokinetic parameters estimated from plasma and blood for TR included: C_{max}, t_{max}, AUC_{24h}. Blood to plasma ratio of TR was also calculated. The percentages of TR excreted in urine ($A_{e\ urine,\ \%dose}$) and feces ($A_{e\ feces,\ \%dose}$) were also determined.

Metabolites were measured in plasma, urine, and feces. Selected samples were pooled for metabolite profiling and identification by liquid chromatographic separation, radioactive detection, and mass spectroscopy.

Safety Evaluation:

Safety and tolerability were evaluated via an assessment of adverse events monitored continuously throughout the study, clinical laboratory tests, 12-lead ECGs, vital signs, physical examinations, and thorough whole body skin examination for potential skin reactions were recorded.

Statistical Methods:

Sample size determination: No formal statistical calculations of sample size were performed. The number of subjects to be included (N=6) is a customary sample size employed in ^{14}C studies and it is expected to allow a meaningful preliminary assessment of the pharmacokinetic and potential metabolite profile.

Pharmacokinetic analyses: Descriptive statistical analyses were provided for the blood, plasma, urine, and fecal TR data. Pharmacokinetic parameters of total radioactivity in blood, plasma, urine, and feces were estimated from concentrations and amounts determined by liquid chromatographic separation, radioactive detection, and mass spectroscopy.

Safety analyses: Safety data was fully listed and summarized with descriptive statistics. All statistical analyses were considered exploratory and interpreted as such.

RESULTS:

All enrolled subjects completed the study. Subjects were healthy white males between 19 to 45 years of age, inclusive with BMI between 18.2 and 25.8 kg/m^2.

PHARMACOKINETIC RESULTS:

Six subjects received a single oral 188 mg dose of ^{14}C-JNJ-28431754 on Day 1 with collection of all urine and feces until 168 hours. The total radioactivity profiles in plasma paralleled those of total radioactivity in blood. The maximum plasma total radioactivity (3,738 ng-eq./mL) were generally attained at about 2 hours postdose. The key pharmacokinetic parameters are summarized below.

Mean (SD) Pharmacokinetic Parameters of ^{14}C-Labeled Moiety in Plasma and Whole Blood and Unchanged JNJ-28431754 in Plasma Following a Single Oral Dose of ^{14}C-JNJ-28431754
(Study 28431754-NAP-1006: Pharmacokinetic Analysis Set)

PK Parameters	Total ^{14}C Plasma (n = 6)	Total ^{14}C Blood (n = 6)
C_{max} (ng-base eq./mL)	3738 (951)	2331 (630)
t_{max} [a] (h)	2.00 (1.50 - 4.00)	1.50 (1.50 - 4.00)
AUC_{24} (ng-base eq.h/mL)	28195 (8150)	16662 (6069)[b]

[a] Median (range)

[b] 4 of 6 subjects have measurable data to 12 hours; AUC_{0-12} is calculated for those subjects, where AUC_{0-12} is the area under the total radioactivity concentration-time curve from 0 to 12 hours after dose administration.

At 1 week after dosing, the total of urinary and fecal excretion of radioactivity amounted to a mean 92.9% of the administered radioactivity (range: 89.7 to 96.0% of the dose). Excretion was mainly via feces; 55.2±5.09% of the total administered radioactivity was found in the fecal extracts, 4.53±1.77% was found in the fecal residues and 0.62±0.73% was found in the lyophilized feces samples. Overall (over 7 days), a total of 60.4±5.73% of the dose was recovered in feces. Urinary excretion averaged 32.5±5.11% of the administered dose (range: 25.7 to 37.7%).

The unchanged drug was the major drug-related component in plasma and accounted from 45.4 to 98.7% of the total drug-derived components in the radiochromatochrams of 0 to 24 hour plasma samples. The remaining drug-derived materials in 1.5 to 12 hour plasma samples were accounted for

by two O-glucuronides of unchanged drug (M7 [16.0 to 28.8%] and M5 [1.9 to 29.6%]) and a hydroxylated metabolite M9 (2.42 to 3.70%). No metabolite was detected in 24-hour plasma samples.

The majority of orally administered dose was recovered in feces. The unchanged drug accounted for an average of 41.5% of the dose excreted in pooled fecal samples while the hydroxylated metabolite M9 and the O-glucuronide metabolite M7 accounted for an average of 7.0% and 3.2% of the excreted dose in feces, respectively.

Overall, the total radioactivity excreted in urine was 32.5% of the dose. The radioactivity in urine could be accounted for by two O-glucuronide metabolites M5 (13.3%) and M7 (17.2%).

SAFETY RESULTS:

Treatment with a single 188 mg dose of JNJ-28431754 was generally well tolerated, with no serious or severe adverse events. There were a total of 4 treatment-emergent adverse events (TEAEs) that occurred in 3 (50%) of 6 subjects. The TEAEs were dry mouth (gastrointestinal disorders), herpes simplex (infections and infestations), increased alanine aminotransferase (investigations), and scab (skin and subcutaneous tissue disorders). All adverse events were of mild severity and either not related or doubtfully related to study drug. All adverse events were resolved except one (skin scab), which was not considered to be related to study drug.

Clinical Laboratory Findings:

There was no indication of any consistent treatment-related effects on clinical laboratory parameters for hematology, biochemistry, and urinalysis parameters. There were no reported incidences of hypoglycemia in this study. One subject had a skin scab that persisted at the time of discharge from the study unit. No follow up was necessary. One subject had an increased alanine aminotransferase (ALT) level that was increased at screening (78 U/L) and on Day 8 (111 U/L). At follow-up, the ALT value increased to 114 U/L (1.6 × ULN) and was considered to be doubtfully related to study drug administration by the investigator and was resolved in 9 days.

Vital Signs and Electrocardiogram:

There were no indications of any treatment-related effect on systolic and diastolic blood pressure or pulse rate, in both supine and standing positions, following oral administration of a single 188 mg dose of ^{14}C-JNJ-28431754 in healthy male subjects. There were no treatment-related changes in the ECG parameters (mean heart rate, PR, QRS, QT interval, QTcB, or QTcF intervals) and morphology after oral administration of ^{14}C-JNJ-28431754.

CONCLUSION:

At one week after dosing, the total of urinary and fecal excretion of radioactivity amounted to a mean 92.9% of the administered radioactivity.

The predominant route of excretion of radioactivity was via the feces. The cumulative excretion of the total radioactivity amounted to 60.4% in the feces and 32.5% in the urine.

JNJ-28431754 was the major radioactive component in feces (41.5%).

O-glucuronide metabolite, M7 (3.2%) and hydroxylated metabolite, M9 (7.0%) were detected in feces at low levels. Metabolite profiles in urine were similar to those in plasma, except that the hydroxylated metabolite, M9 was not detected in urine.

Unchanged drug (JNJ-28431754) was the major radioactive component in plasma and the remaining drug-derived materials in plasma were accounted for by two major *O*-glucuronides of unchanged drug (M7 and M5) and a minor hydroxylated metabolite M9.

JNJ-28431754 was well tolerated following a single 188 mg oral dose of JNJ-28431754.

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