# SYNOPSIS

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| Name of Sponsor/Company | Johnson & Johnson Pharmaceutical Research & Development, L.L.C. |
| Name of Finished Product | N/A |
| Name of Active Ingredient(s) | JNJ-28431754 |

**Protocol No.:** 28431754NAP1008

**Title of Study:** A Double-Blind, Randomized, Placebo-Controlled, Sequential Cohort Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Oral Doses of JNJ-28431754 in Otherwise Healthy Obese Male and Female Subjects.

**Principal Investigator:** Maria J. Gutierrez, M.D. Comprehensive Phase One™ (A Division of Comprehensive Neuroscience) [redacted]

**Publication (Reference):** None.

**Study Period:** First subject admitted to clinic for baseline measurements on 14 June 2007 with the last scheduled subject follow visit up on 30 October 2007. Database lock was on 15 November 2007. One subject required follow up lab work that resulted in the last unscheduled follow up visit on 5 December 2007.

**Phase of Development:** Phase 1

**Objectives:**

The objectives were to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of JNJ-28431754 after multiple ascending oral doses of JNJ-28431754 in otherwise healthy obese male and female subjects. Key pharmacodynamic endpoints include the amount of glucose excreted in urine and appetite and satiety as assessed with a visual analogue scale (VAS) questionnaire.

**Methods:**

- This was a single-center, randomized, double-blind, placebo-controlled, multiple ascending dose (14 day) study with 5 sequential cohorts, each with 16 otherwise healthy obese male and female subjects who satisfied the study inclusion-exclusion criteria. In each cohort 12 and 4 subjects were randomized to JNJ-28431754 or placebo, respectively. In the first 4 cohorts, JNJ-28431754 dose levels were 30, 100, 300 and 600 mg once daily, respectively; 300 mg twice daily was administered in the 5$^{th}$ cohort.
- Subjects were screened within 28 days of Day 1. Eligible subjects were placed on a dietitian-guided weight maintaining diet (approximately 55 to 60% of total calories as carbohydrate, 10 to 20% protein, and approximately 30% fat, with total daily caloric intake individually adjusted for resting metabolic rate [RMR]), beginning 15 days prior to Day 1 (Day- 15) and continuing throughout the entire study until completion of the follow-up visit.
- Subjects were admitted to the Clinical Research Unit (CRU) on Day –3. They received placebo once daily on Day –2 and Day –1 in a single blind fashion (subjects were blinded) and underwent baseline safety and PD assessments. Eligible subjects were randomized to a double-blind treatment with JNJ-28431754 or placebo, once daily or twice daily on Days 1 to 14. Subjects were discharged from the CRU on Day 18 (96 hours post last dose) and returned to the CRU for safety assessments and PK sample collections on the mornings of Days 19 and 20. Final follow-up visits were conducted within 7 to 10 days after the Day 20 visit.

**Number of Subjects (planned and analyzed):**

A total of 80 subjects were planned and analyzed in this study. For each cohort; 30, 100, 300, 600 mg once daily, and 300 mg twice daily, 12 subjects were administered JNJ-28431754 at least once, for a total of 60 subjects, and 4 subjects were administered placebo, for a total of 20 subjects. The total number of subjects that participated in the study was 80; 60 were given JNJ-28431754 and 20 were given placebo.

**Diagnosis and Main Criteria for Inclusion:**

Males and postmenopausal/surgically sterile females, age 18 to 60 years inclusive, with a body mass index (BMI) between 30.0 and 39.9 $kg/m^2$ inclusive (BMI = weight/$height^2$), nondiabetic, nontobacco users were enrolled. An equal number of men and women in each cohort were targeted for enrollment. Subjects with well-controlled hypertension on a stable antihypertensive drug and/or on a stable regimen of dyslipidemic medications were not excluded.

**Test Product, Dose and Mode of Administration, Batch No.:**

JNJ–28431754, a white powder with very low aqueous solubility, was compounded per the protocol-specified dispensing procedure to obtain a liquid suspension of concentration 5 mg/mL (Lot No. R14586) or 50 mg/mL (Lot No. R14587) in 0.5% hypromellose, and was dispensed using a standard, syringe-like oral dispenser (Exacta-Med®). JNJ-28431754 and matching placebo were stored between 2ºC and 8ºC, protected from white light. Dose levels tested were: 30, 100, 300, 600 mg once daily (administered between ~8 and 9 AM) and 300 mg twice daily (administered between ~8 and 9 AM and between ~6 and 7 PM).

**Reference Therapy, Dose and Mode of Administration, Batch No.:**

A placebo [an aqueous solution of 0.5% weight/weight (w/w) hypromellose (Methocel)] for JNJ-28431754 was used as reference. (Lot No. R14588).

**Duration of Treatment:** The duration of dosing with study medication was a total of 16 days with single blind placebo dosed on Days -1 and -2 and double blind (treatment with JNJ-28431754 or placebo) on Days 1 to 14. Total study duration for each subject was about 8 weeks starting with screening and through the pretreatment diet run-in, treatment period, and poststudy follow-up periods.

**Criteria for Evaluation:**

Pharmacokinetic Evaluations: Plasma and urine samples were collected for measurement of JNJ-28431754 and its metabolites [JNJ-41488525 (M7) and JNJ-41980874 (M5)] concentrations as specified in the Time and Events Schedule, which is given following the synopsis of the Study Protocol.

Pharmacokinetic plasma and urine samples were planned to be 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 JNJ-41488525 (M7) and JNJ-41980874 (M5) in subset of subjects (n=6) at 100 mg and 400 mg doses once daily 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: $C_{min}$, $C_{avg}$, $C_{max}$, $t_{max}$, $C_{last}$, $t_{last}$, $AUC_{0-12}$, $AUC_{0-24h}$, $AUC_{\tau}$, $AUC_{last}$, $AUC_{\infty}$, $\lambda_z$, $t_{½}$, FI, Acc. Ratio. Pharmacokinetic parameters estimated from urinary excretion data included: $Ae_{0-24}$ and $Ae_{0-24}$ (% Dose).

Pharmacodynamics Evaluations: Pharmacodynamic analyses included evaluation of urine glucose levels and plasma glucose, insulin, and C-peptide levels. Blood samples were also collected for possible measurement of incretins and other hormones {eg, glucagon-like peptide-1 (GLP-1) [active and/or total], gastric inhibitory polypeptide (GIP) [active and/or total], peptide YY (PYY), adiponectin, oxyntomodulin, and/or ghrelin}. Visual analogue scale questionnaires were used to assess subjective appetite ratings. Morning fasting body weights were also assessed.

Safety and Tolerability Evaluations: Safety and tolerability were evaluated via assessment of adverse events monitored continuously throughout the study, and clinical laboratory tests, 12-lead electrocardiogram (ECGs), vital signs, physical examinations (including whole body skin examinations), and the frequency of urination at scheduled time-points from screening to follow-up.

## Statistical Methods:

- Pharmacokinetic analyses of the metabolites [JNJ-41488525 (M7) and JNJ-41980874 (M5)] were performed for subjects who received either 100 or 600 mg doses of JNJ-28431754. Results were summarized and descriptive statistics were generated for both the 100 and 600 mg dose levels.
- Pharmacodynamic analyses, which included the percentage, change from baseline for amount of glucose excreted in urine (0 to 24 hours) was analyzed by fitting a mixed effect linear model for comparison of dose versus placebo. The VAS scores for subjective appetite ratings were analyzed using a mixed effects model. Mixed effect ANOVA modeling was used to assess treatment effects on plasma glucose levels. The estimated least-squares means and appropriate 95% confidence intervals (CI) for the difference of the mean pharmacodynamic parameters were obtained for pharmacodynamic evaluations.
- All safety data were listed. All statistical analyses were considered exploratory and interpreted as such. No corrections were made for multiple comparisons.
- The sample size, the number of subjects, included (N = 16 per cohort) was selected to allow appropriate clinical judgment of safety and tolerability and also to allow a meaningful assessment of pharmacokinetic parameters and pharmacodynamic effect. The sample size was chosen to provide 80% power to detect a 70% difference in urinary glucose excretion (UGE: 0 to 24 hour total; UGE) compared to placebo using a coefficient of variation (CV) of 50% with a 1-sided alpha of 0.05. The sample size of 16 per cohort also was chosen to provide 80% power to detect a 38% change compared to placebo in hunger reported using a VAS on a 100 mm scale and a CV of 30.5% with a 2-sided alpha of 0.1. In addition, the sample size of 16 subjects per cohort also was estimated to also provide 80% power to detect a 17.5% reduction in 24-hour mean plasma glucose AUC, compared to placebo, assuming a 1-sided test and a CV of 18%.

**RESULTS:**

- All 80 (100%) of subjects enrolled in the study completed the study. One subject was not dosed on Day 14 but did complete all safety assessments.

DEMOGRAPHICS AND BASELINE CHARACTERISTICS:

- Out of a total of 80 subjects, there were 40 men and 40 women, 67 of whom self-reported as being white, 12 as black, and 1 as other (American Indian). The groups were well balanced and there were no large differences in mean age, weight, BMI, baseline glomerular filtration rate (GFR) or baseline plasma glucose levels.

PHARMACOKINETIC RESULTS:

A subset of the total dose group population (six subjects from the 100 mg dose group and six subjects from the 600 mg dose group) were analyzed to determine JNJ-41488525 (M7) and JNJ-41980874 (M5) plasma concentrations.

Median $t_{max}$ values of 3 to 4 hours were observed for metabolite JNJ-41488525 (M7) on Day 1 and 1.75 to 2 hours on Day 14. JNJ-41980874 (M5) had median $t_{max}$ values of 4 hours on Day 1 and Day 14 for both dose groups. Mean $C_{max}$ values for JNJ-41980874 (M5) and JNJ-41488525 (M7) on Day 1 increased by a ratio of 5.2:1 and 7.5:1, and on Day 14 increased by a ratio of 4.9:1 and 5.7:1

when dosed with 600 mg JNJ-28431754 compared to 100 mg. The corresponding mean $AUC_{\tau}$ values increased by the ratios of 5.4:1 and 7.2:1 on Day 1, and 4.9:1 and 5.6:1 on Day 14.

Accumulation was assessed by the ratio of $AUC_{0-24h}$ values between Day 14 and Day 1 (i.e., the multiple-dose to single-dose ratio). There was a mean 1.09 to 1.16-fold accumulation following multiple dosing at 100 and 600 mg for JNJ-41488525 (M7), suggesting no significant accumulation. Modest accumulation of JNJ-41980874 (M5) was evident after multiple dosing with 100 mg once daily (accumulation ratio: 1.46) and 600 mg once daily (accumulation ratio: 1.59). Mean $t_{1/2}$ values ranged from 16.8 to 19 hours for metabolites M5 and M7 on Day 14.

After multiple doses of 100 and 600 mg, 16.4 and 14.4% of the administered dose was recovered as JNJ-41488525 (M7), and 8.38 and 8.63% of the administered dose was recovered as JNJ-41980874 (M5) in the urine.

Mean (SD) Day 1 Plasma Pharmacokinetic Parameters of JNJ-41980874 and JNJ-41488525 in Study 28431754-NAP-1008

| Day 1 | JNJ-41488525 (M7) | | JNJ-41980874 (M5) | |
|---|---|---|---|---|
| PK Parameters | 100 mg (n = 6) | 600 mg (n = 6) | 100 mg (n = 6) | 600 mg (n = 6) |
| $C_{max}$ (ng/mL) | 380 (109) | 2,845 (681) | 371 (163) | 1,925 (614) |
| $t_{max}$[a] (h) | 4.00 (2.00-12.00) | 3.00 (1.48-6.00) | 4.00 (1.50-12.00) | 4.00 (3.98-6.00) |
| $t_{last}$[a] (h) | 12.00 (12.00-12.00) | 12.00 (11.98-12.00) | 12.00 (12.00-12.00) | 12.00 (11.98-12.00) |
| $AUC_{0-12}$ (ng.h/mL) | 2,600 (644) | 21,591 (5,959)[b] | 2,381 (962) | 15,372 (3,171)[b] |
| $AUC^{c}_{0-24}$ (ng.h/mL) | 3,854 (1,083)[b] | 27,634 (6,951) | 3,786 (2,133)[b] | 20,505 (4,873) |
| $AUC_{\infty}$ (ng.h/mL) | 4,929 (2328) | 31,415 (10,615) | 5,721 (5,850) | 25,191 (9,793) |
| $t_{1/2}$ (h) | 8.3 (4.2)[b] | 6.7 (4.7) | 8.1 (6.2)[b] | 8.3 (6.5) |
| $\lambda z$ (1/h) | 0.108 (0.0610)[b] | 0.128 (0.0445) | 0.116 (0.0560)[b] | 0.116 (0.0549) |
| $C_{max}$/D (ng/mL/mg) | 3.80 (1.09) | 4.74 (1.14) | 3.71 (1.63) | 3.21 (1.02) |
| $AUC_{0-12}$/D (ng.h/mL/mg) | 26.0 (6.44) | 36.0 (9.93)[b] | 23.8 (9.62) | 25.6 (5.28)[b] |
| $AUC^{c}_{0-24}$/D (ng.h/mL/mg) | 38.5 (10.8)[b] | 46.1 (11.6) | 37.9 (21.3)[b] | 34.2 (8.12) |
| $AUC_{\infty}$/D (ng.h/mL/mg) | 49.3 (23.3)[b] | 52.4 (17.7) | 57.2 (58.5)[b] | 42.0 (16.3) |

[a] Median (Range)
[b] n = 5
[c] $AUC_{0-24}$ value is extrapolated from 0-12 hours data

Mean (SD) Day 14 Plasma Pharmacokinetic Parameters of JNJ-41980874 and JNJ-41488525 in Study 28431754-NAP-1008

| Day 14 | JNJ-41488525 (M7) | | JNJ-41980874 (M5) | |
|---|---|---|---|---|
| PK Parameters | 100 mg (n = 6) | 600 mg (n = 6) | 100 mg (n = 6) | 600 mg (n = 6) |
| $C_{min}$ (ng/mL) | 92.8 (68.4) | 539 (210) | 167 (148) | 710 (206) |
| $C_{max}$ (ng/mL) | 423 (128) | 2412 (427) | 528 (279) | 2,572 (575) |
| $t_{max}$[a] (h) | 1.75 (1.50-6.00) | 2.00 (2.00-4.00) | 4.00 (1.00-10.00) | 4.00 (1.50-10.00) |
| $t_{last}$[a] (h) | 72.00 (48.00-120.00) | 132.00 (72.00-144.00) | 84.00 (48.00-120.00) | 132.00 (72.00-144.00) |
| $AUC_{0-12}$ (ng.h/mL) | 3,579 (1,488) | 19,921 (4,996) | 4,115 (2,225) | 21,342 (4,855) |
| $AUC_{\tau}$ (ng.h/mL) | 5,421 (2,699) | 30,105 (8,544) | 6,582 (4,044) | 32,187 (7,935) |
| $AUC_{last}$ (ng.h/mL) | 7,495 (4,406) | 48,489 (19,215) | 10,808 (8,390) | 54,347 (16,471) |
| $t_{1/2}$ (h) | 18.0 (10.5) | 19.0 (6.5) | 17.4 (6.5) | 16.8 (6.4) |
| $\lambda_z$ (1/h) | 0.0498 (0.0244) | 0.0403 (0.0140) | 0.0455 (0.0188) | 0.0467 (0.0183) |
| FI (%) | 164 (64.6) | 158 (46.2) | 143 (27.4) | 145 (44.2) |
| Acc. Ratio[c] | 1.16 (0.193)[b] | 1.09 (0.137) | 1.46 (0.391)[b] | 1.59 (0.357) |
| $Ae_{0-24}$ (mg) | 22.4 (4.19) | 118 (12.9) | 11.5 (2.51) | 70.8 (15.7) |
| $Ae_{0-24}$ (% Dose) | 16.4 (3.07) | 14.4 (1.57) | 8.38 (1.84) | 8.63 (1.91) |

[a] Median (Range)
[b] n = 5
[c] Acc. Ratio = $AUC_{\tau}$ (Day 14) /$AUC_{0-24}$ (Day 1)

PHARMACODYNAMIC RESULTS:

Urine Glucose Excretion: JNJ-28431754 treatment increased UGE relative to predose baseline (Day -1) and also relative to placebo treatment, in a dose-dependent manner. The elevation of mean urine glucose excretion ($UGE_{0-24h}$) observed on Day 1 was largely maintained over the ensuing 14-day dosing period for all the dose levels studied. The maximal mean $UGE_{0-24h}$ of 47 to 50 g on Day 14 at the 300 and 600 mg once daily dose levels suggests apparent saturation of $UGE_{0-24h}$ following single daily doses ≥300 mg once daily.

Mean (SD) 24-Hour UGE (g) With Multiple Doses of JNJ-28431754 in Otherwise Healthy Obese Subjects

| Day | 30 mg N=12 | 100 mg N=12 | 300 mg N=12 | 600 mg N=12 | 300 mg b.i.d. N=12 | Placebo N=20 |
|---|---|---|---|---|---|---|
| Day -1 | 0.24 (0.26) | 0.23 (0.55) | 0.060 (0.024) | 0.053 (0.016) | 0.115 (0.127) | 0.087 (0.047) |
| Day 1 | 3.17 (3.98) | 35.5 (10.8) | 53.2 (19.4) | 64.1 (32.1) | 74.2 (10.6) | 0.52 (1.45) |
| Day 7 | 10.5 (5.98) | 32.6 (13.3) | 49.8 (27.1) | 45.2 (13.5) | 65.7 (18.5) | 0.077 (0.049) |
| Day 14 | 9.15 (4.16) | 33.2 (9.72) | 47.0 (23.3) | 50.4 (13.0)[a] | 61.2 (16.1) | 0.087 (0.035) |
| Day 15 | 1.38 (0.98) | 11.3 (8.11) | 35.1 (20.2) | 39.0 (14.0)[a] | 47.7 (19.6) | 0.071 (0.049) |
| Day 16 | 0.26 (0.31) | 4.67 (6.00) | 16.1 (20.0) | 29.0 (13.1)[a] | 34.0 (19.1) | 0.051 (0.043) |
| Day 17 | 0.17 (0.27) | 1.28 (1.94) | 6.19 (10.1) | 14.8 (13.3)[a] | 22.1 (15.8) | 0.069 (0.063) |

[a] N = 11 Subject [redacted] was not dosed on Day 14
Note: placebo dosed on Day –1, first JNJ-28431754 dose on Day 1 and last dose on Day 14
(g) = grams; b.i.d. = twice daily

Plasma Glucose: While some statistically significant reductions ($p<0.05$) in 24-hour mean glucose levels and fasting glucose levels were detected in certain dose groups, relative to the placebo group, there was no consistent reduction or any suggestion of a dose-response. The plasma glucose levels following breakfast (0 to 4 hours) on Days 1 and 14 showed an apparent decrease in peak levels and $AUC_{0-4}$ in all groups relative to Day -1. There was no meaningful difference in glucose absorption ($AUC_{0-2h}$) following breakfast given 5 to 10 minutes after dosing (Days 1 and 14) compared to breakfast given 30 minutes after dosing (Day 11).

Plasma Insulin: While some statistically significant reductions ($p <0.05$) in 24-hour mean insulin levels and fasting plasma insulin levels were detected in certain dose groups, relative to the placebo group, there was no consistent reduction or any suggestion of a dose-response. The plasma insulin levels following breakfast (0 to 4 hours) on Days 1 and 14 showed an apparent decrease in peak levels and $AUC_{0-4h}$ in all treated groups relative to Day –1. There was no meaningful difference in insulin exposure ($AUC_{0-2h}$) following breakfast given 5 to 10 minutes after dosing (Days 1 and 14) compared to breakfast given 30 minutes after dosing (Day 11).

Plasma C-Peptide: While some statistically significant reductions ($p <0.05$) in 24-hour mean C-peptide levels were detected in certain dose groups, relative to the placebo group, there was no consistent reduction or any suggestion of a dose-response.

Plasma Total GLP-1: There was a statistically significant increase in GLP-1 $AUC_{0-2h}$ as compared to placebo for the 100 and 300 mg dose groups on Day 1 (20 and 47%, respectively) and for the 300 mg dose group on Day 14 (64%).

Renal Thresholds:. The renal threshold was lowered in a dose-dependent fashion on both Day 1 and Day 14, with maximally-effective doses lowering $R_T$ to approximately 60 mg/dl. These results are similar to what was observed in healthy subjects suggesting that the pharmacodynamic effects of the drug to lower the renal threshold are similar in both lean healthy subjects and obese nondiabetic subjects.

Insulin Secretion Rate: While some statistically significant differences in insulin secretion rate (calculated using C-peptide concentrations and a deconvolution method) were detected in the 100 mg once daily and 300 mg twice daily dose groups, there was no consistent reduction in insulin secretion or any suggestion of a dose-response.

Body Weight: The placebo-subtracted change in mean body weight on Day 14 versus Day -1 was -1.5, -1.3, -0.7, -2.1 and -2.2 kg in the 30, 100, 300, 600 mg once daily, or 300 mg twice daily dose groups, respectively. These reductions in placebo-subtracted change in mean body weight on Day 14 versus Day -1 were statistically significant ($p < 0.05$) in all dose groups except for the 300 mg once daily dose group ($p = 0.129$). The placebo-subtracted percent change in mean body weight (kg) on Day 14 versus Day -1 was -1.8, -1.5, -1.0, -2.2, and -2.0 % in the 30, 100, 300, 600 mg once daily, or 300 mg twice daily dose groups, respectively. These reductions were statistically significant ($p < 0.05$) in all dose groups.

Appetite and Satiety: While some statistically significant differences in mean subjective appetite VAS scores (eg, How satisfied do you feel?, 600 mg cohort only) were detected, there were no consistent trend in these subjective parameters (questions asked) or any suggestion of a dose-response.

SAFETY RESULTS:

Treatment with JNJ-28431754 at doses up to 600 mg administered once daily or at a dose of 300 mg administered twice daily for 14 days was generally well tolerated, with no serious or severe adverse events. All adverse events were of mild or moderate severity.

There was 1 discontinuation from treatment due to an adverse event: 1 subject who was receiving 600 mg once daily was discontinued from dosing on Day 14 due to a rash of moderate severity that appeared on Day 13. The rash resolved without treatment and did not recur.

All adverse events were resolved at the end of the study except for 1 subject who received 300 mg twice daily and developed a skin abnormality on Day 16, diagnosed by a consulting dermatologist as pityriasis rosea. This adverse event was persisting at the time of final follow-up visit with no further investigations.

The most frequently reported TEAEs (number of subjects with at least 1 reported AE) were mild GI disorders (20% of the placebo group subjects and 17, 17, 0, 50, and 33% of the 30, 100, 300, 600 mg once daily, and 300 mg twice daily group subjects, respectively), and skin findings (5% of the placebo group subjects and 17, 25, 17, 42, and 17% of the 30, 100, 300, 600 mg once daily, and 300 mg twice daily group subjects, respectively).

The incidence of TEAEs by relationship to study drug are as follows: Constipation was considered to be possibly related to study drug in 11 subjects and not related in 1 subject receiving JNJ-28431754, and 4 subjects receiving placebo (when blinded). Rash was considered to be not related to study drug in 2 subjects, doubtfully related in 1 subject, possibly related in 1 subject, probably related in 3 subjects, and very likely related in 1 subject receiving JNJ-28431754. Subjects receiving placebo did not report any rash. Pruritus was considered to be possibly related as well probably related to the study drug in 2 subjects each receiving JNJ-28431754. Headache was considered to be not related to the study drug in 1 subject and possibly related in 4 subjects receiving JNJ-28431754, and possibly related in 1 subject receiving placebo (when blinded). An increase in plasma creatine kinase levels was thought to be doubtfully related to the study drug in 2 subjects and possibly related in 1 subject receiving JNJ-28431754.

There were no reports of symptomatic or asymptomatic hypoglycemia in this study.

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

Patient reported outcome data related to urination frequency collected on Days –2, 4, 7, and 15 did not indicate any apparent differences between the placebo group and the JNJ-28431754 groups as well as between the 30, 100, 300, and 600 mg once daily and 300 mg twice daily doses of JNJ-28431754.

STUDY LIMITATIONS:

While statistically significant weight loss was observed in this study, the study subjects were receiving an individual RMR-adjusted, fixed-calorie, and weight maintaining diet during their in-house stay. The effect of JNJ-28431754 on body weight loss in a free-living outpatient environment and over a longer time period needs to be investigated in order to better assess the actual weight loss potential of JNJ-28431754.

CONCLUSION:

- JNJ-28431754 was well tolerated with oral doses of 30 to 600 mg once daily, and 300 mg twice daily for 14 consecutive days in otherwise healthy male and female obese subjects.
- Plasma $C_{max}$ and AUC of JNJ-28431754 metabolites (M5 and M7) increased almost proportionately with the dose (100 mg to 600 mg).
- $T_{max}$ and $t_{1/2}$ of JNJ-41980874 (M5) and JNJ-41488525 (M7) were independent of the dose.
- JNJ-28431754 treatment increased UGE relative to predose baseline (Day -1) and also relative to placebo treatment, in a dose-dependent manner.
- There was no apparent dose-response or change in mean plasma glucose, insulin or C-peptide levels following multiple dosing with JNJ-28431754. There was a statistically significant increase in GLP-1 total levels compared to placebo for the 100 mg and 300 mg dose groups on Day 1 (20% and 47%, respectively) and for the 300 mg dose group on Day 14 (64%).
- Statistically significant reductions in placebo-subtracted percent bodyweight of -1.0 to -2.2% were detected in all dose groups.

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