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.: 28431754DIA1010

Title of Study: A Randomized, Double-Blind, Double-Dummy, Placebo- and Positive-Controlled, Four-Way Crossover Study Evaluating Electrocardiogram Intervals in Healthy Adults Receiving a Single, Oral Dose of JNJ-28431754 at Therapeutic and Supra-Therapeutic Doses

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Publication (Reference): None

Study Period: 16 July 2008 to 5 September 2008; final database lock: 08 November 2008

Phase of Development: 1

Objectives: The primary objective was to assess the effects of JNJ-28431754 on the measured QT interval and QT interval corrected for heart rate (QTc) in healthy adults. Secondary objectives were to assess the safety and tolerability of JNJ-28431754, characterize the single-dose pharmacokinetics (PK) of JNJ-28431754 and document exposure with the 300- and 1,200-mg doses of JNJ-28431754 and to describe the effect of JNJ-28431754 on other 12-lead (electrocardiogram) ECG parameters (e.g., QRS, PR intervals).

Methods: This study was a randomized, double-blind, placebo- and positive-controlled, double-dummy, 4-way crossover, single-center study of oral JNJ-28431754 at therapeutic (300 mg) and supratherapeutic (1,200 mg) doses, administered as single doses, in healthy adults. Moxifloxacin (a single 400-mg oral dose) was used as a positive control for the evaluation of QT/QTc interval prolongation. There were 3 study phases: a 20-day screening phase, a double-blind treatment phase (4 treatment periods with a minimum 10 day washout between Day 1 of each treatment period), a post-treatment phase (end-of-treatment procedures on Day 2 of Period 4 or at the time of early withdraw). The total duration of the study was approximately 61 days, including a 20-day pretreatment period and 5- to10-day followup. Each subject received each of the following 4 treatments, 1 in each period, in 1 of the 4 randomly determined sequences detailed in the table below: Treatment A, JNJ-28431754 300 mg (therapeutic dose); Treatment B, JNJ-28431754 1,200 mg (supratherapeutic dose); Treatment C, Placebo; and Treatment D, moxifloxacin 400 mg.

Overview of Treatment Sequences

Sequence	Period 1	Period 2	Period 3	Period 4
1	A	D	B	C
2	B	A	C	D
3	C	B	D	A
4	D	C	A	B

Number of Subjects (planned and analyzed): Approximately 60 healthy subjects (men and women) were to have been randomized into the study to ensure that at least 52 subjects completed the study. A total of 60 subjects were randomly assigned to study treatment; 55 subjects completed the study; all 60 subjects

were included in the safety analysis set and pharmacodynamic (PD) analysis set; and 56 subjects were included in the PK analysis set.

Diagnosis and Main Criteria for Inclusion: Healthy men and women between 18 and 55 years of age (inclusive), with a body mass index (BMI) between 18 and 30 kg/m² (inclusive), and a body weight of not less than 50 kg, a normal 12-lead ECG (normal sinus rhythm and normal QTc, QRS, and PR intervals) determined at screening, and no history of a cardiovascular disease, were eligible for enrollment.

Test Product, Dose and Mode of Administration, Batch No.: JNJ-28431754 was administered as 100 and 200 mg overencapsulated oral tablets (lot nos: PD2779 and PD2780, respectively).

Reference Therapy, Dose and Mode of Administration, Batch No.: Moxifloxacin, was administered as an overencapsulated 400 mg oral tablet (lot no: PD2867). Overencapsulated placebo to match JNJ-28431754 was administered (lot no: PD2776).

Duration of Treatment: Four single doses, each from among 1 of 4 different treatments (JNJ-28431754 300 mg, JNJ-28431754 1,200 mg, placebo and moxifloxacin 400 mg), 1 dose in each of the 4 treatment periods, in 1 of 4 randomly determined sequences.

Criteria for Evaluation:

Pharmacokinetics: Blood samples for PK analysis were collected within 5 minutes after each timepoint up to 24-hours postdose on Day 2 of each of the 4 periods). 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 at the Sponsor's bioanalytical laboratory in Beerse, Belgium. PK parameters estimated from plasma were: C_{max}, t_{max}, AUC_{24}.

Moxifloxacin plasma concentrations at 3 hours were assayed using a validated and specific LC-MS/MS method at the bioanalytical lab of PPD in [redacted].

Pharmacodynamics: ECG parameters evaluated for the purpose of pharmacodynamic (PD) assessment included QT intervals extracted from continuous 12-lead ECG Holter recordings and QTc intervals. At several timepoints (predose through to 24-hours postdose on Day 1 of each of the 4 periods), 10-second digital 12-lead ECG tracings were extracted from ECG Holter monitors in triplicate by the central ECG laboratory. At each timepoint, the average of the triplicate ECG measurements was taken and used for the analysis. The measured QT intervals were corrected for heart rate using 3 methods of correction (Fridericia's, Bazett's, and Study Specific Power methods). When ECG extraction and PK sample collection was scheduled at the same nominal timepoint, the timing of the PK blood sample collection coincided with, i.e., occurred within approximately 1 minute after the last scheduled triplicate ECG Holter extraction.

Pharmacogenomics: A single pharmacogenomic blood sample (10mL) was taken from all subjects predose in Period 1 only. Upon the observation of irregular QT/QTc intervals during the study, this pharmacogenomic blood sample was used for its primary purpose, the analysis of genetic variants in 5 ion channel genes that have been associated with irregular QT/QTc intervals. The DNA samples were also to be analyzed for additional genes related to cardiovascular safety, or to the PK, PD, or safety/tolerability of JNJ-28431754 during the study, as necessary.

Safety: Safety and tolerability were evaluated via an assessment of adverse events monitored continuously throughout the study, and clinical laboratory tests (coagulation, hematology and serum chemistry), vital signs (oral temperature, pulse, and blood pressure), physical examinations, and single 12-lead ECGs evaluated at screening and the end of the study (or the time of early withdraw). Hypoglycemia was monitored throughout the in-house period.

Statistical Methods:

Sample Size: Based on previous J&JPRD studies, the intrasubject standard deviation (SD) for the largest mean change from baseline QTc based on the primary correction method (ΔQTc) (see related discussion

under PD below) was assumed to be 10 ms. Using a SD of 10 ms, for a sample size of 52 subjects, the probability that the upper limit of the 2-sided 90% confidence interval (CI) (1-sided upper 95% CI) for the difference in mean ΔQTc between JNJ-28431754 and placebo (ΔΔQTc) at each timepoint would fall below 10 ms was estimated to be 80%, when the true difference in means equaled 5 ms. With an intra-subject SD of 10 ms and a sample size of 52 subjects, the probability that the lower limit of the 2-sided 90% CI (1-sided lower 95%CI) for the difference in mean ΔQTc between moxifloxacin and placebo (ΔΔQTc) would be greater than 5 ms was estimated to be 80%, when the true difference in means was greater or equal to 10 ms.

Pharmacokinetics: Plasma JNJ-28431754 concentration-time profiles for each subject and mean plasma concentration-time profiles were plotted, plasma concentration data at each timepoint were summarized by descriptive statistics, and PK parameters were summarized. Observed plasma concentrations of moxifloxacin at 3 hours postdose on Day 1 were summarized.

Pharmacodynamics: The primary correction method for QT intervals was based on an evaluation of baseline (QTc, RR) data for the 3 correction methods (Fridericia's, Bazett's, and Study-specific Power methods). The primary method to correct QTc for heart rate for statistical analysis was the method that yielded the smallest correlation between QT corrected for heart rate (QTc) and RR evaluated on baseline data. All 12-lead ECG variables and their changes from baseline were listed and summarized with descriptive statistics. ECG variables versus time plots were generated.

The primary PD parameter of interest for statistical analysis was the change from baseline in QTc (ΔQTc). The difference in ΔQTc between each dose of JNJ-28431754 or moxifloxacin and placebo (ΔΔQTc) was summarized by treatment and timepoint. Mixed-effect models were fitted to the data with ΔQTc as the dependent variable, and sequence, treatment, period, timepoint of measurement, and treatment by timepoint of measurement interaction as factors and subject as a random effect. Using the least-square means and estimated intrasubject variance, 90% CI were calculated for the difference in means between each dose of JNJ-28431754 versus placebo at each timepoint of measurement, and (Bonferroni-adjusted) 97.5% CI for moxifloxacin versus placebo were calculated at 1.5, 2, 3, and 4 hours after dosing. The null hypothesis was to be rejected if the upper limit of the 2-sided 90% CI for the difference in mean between each dose of JNJ-28431754 and placebo fell below 10 ms at all timepoints. Assay sensitivity was established if the lower limit of the 97.5% 2-sided CI for the difference in mean ΔQTc between moxifloxacin and placebo exceeded 5 ms at 1 or more of 4 selected timepoints of measurement.

The incidence count and percentage of subjects with a QTc increase ≥30 and ≥60 ms were tabulated for each treatment; the incidence counts and percentages for each sex were also reported. The incidence count and percent of subjects with any postdose QTc values <320, <360, <450 ms and >450, >480 and >500 ms, was be tabulated for each treatment, and the incidence counts and percentages for each sex was also reported. QRS and PR were summarized using descriptive statistics. The incidence count and percent of subjects with treatment-emergent T-wave and U-wave and other morphologic findings were tabulated for each treatment.

Pharmacokinetics/Pharmacodynamics: The PK/PD evaluations were based on data extracted from the continuous 12-lead ECG recordings and plasma concentration data (see separate discussion of PK and PD above) after JNJ-28431754 and placebo administration. Data collected after moxifloxacin administration was not used in this analysis. Consistent with the ICHE14 guideline (2005) for conducting QT/QTc studies and a specific U.S. Food and Drug Administration request, a study-specific inter-reader ECG reliability assessment was conducted by the central ECG vendor (MDS Pharma Services, Inc.). The ΔQTc at each timepoint of measurement was plotted against the corresponding plasma concentration of JNJ-28431754 to describe the relationship between the plasma concentration of JNJ-28431754 and the change from baseline in QTc interval for the JNJ-28431754 treatment. Placebo was included in the graphs with a plasma concentration of 0. A linear mixed-effects model was fit to the ΔΔQTc data from both doses of JNJ-28431754 with concentration as a predictor and subject as a random effect (intercept and slope); if the intercept effect was not significant, the model was to be re-fit with a zero intercept term. The predicted value of ΔΔQTc (along with 90% CI) was to be estimated at the mean C_{max} values for each dose of JNJ-28431754.

Safety: Safety was evaluated by examining the incidence and type of adverse events and changes in clinical laboratory test values, physical examination results, single 12-lead ECGs, and vital sign from the screening phase through to study completion.

RESULTS:

A total of 60 subjects met the eligibility criteria and were enrolled in the study, received at least 1 dose of study drug (JNJ-28431754, moxifloxacin or placebo), and were included in the safety analysis set. Fifty-five (92%) of the 60 subjects enrolled completed the study. The reasons for withdrawal included adverse events (3 subjects) and other reasons (2 subjects).

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:

All 60 subjects included in the safety analysis set had at least 1 PD measurement after dosing and were included in the PD analysis set. Data from 56 subjects who received 300 mg JNJ-28431754 and 55 subjects who received 1,200 mg JNJ-28431754 were included in the PK analysis and descriptive statistics for JNJ-28431754 plasma concentrations.

Pharmacokinetics

Systemic exposure (AUC_{24}) and peak concentration (C_{max}) increased with increasing dose of JNJ-28431754. For a 4-fold increase in dose, the arithmetic mean C_{max} and AUC_{24} increased by approximately 3-fold.

Summary of Mean(SD) JNJ-28431754 Pharmacokinetic Parameters
(Study JNJ-28431754DIA1010: Pharmacokinetic Analysis Set)

Pharmacokinetic Parameters	300 mg (N=56)	1,200 mg (N=55)
C_{max} (ng/mL)	2408 (565)	6408 (2034)
t_{max} (h)[a]	2.05 (1.05-5.07)	3.05 (1.55-6.05)
AUC_{24} (ng·h/mL)	18857 (4094)	61196 (17789)

[a] median (range)

For the 58 subjects receiving 400 mg moxifloxacin, the mean (SD) moxifloxacin plasma concentration was 2,152 (472) ng/mL (3 hours postdose).

Pharmacodynamics

The study specific power correction method (QTcP) yielded the smallest correlation with RR. In addition, the upper limit of 95% CI for the estimated slope of the regression line was lowest for the study-specific correction method. Therefore, QTcP was used as the primary method to correct QT for heart rate in the statistical analysis.

Summary of Mixed Effects Linear Regression Analysis to Determine the Primary Correction Method
(Study JNJ-28431754DIA1010: Pharmacodynamic Analysis Set)

Correction	Estimated Slope	SE of the Estimated Slope	95% CI
QTcB (ms)	-0.2252	0.0113	(-0.2478 , -0.2025)
QTcF (ms)	-0.0588	0.0112	(-0.0814 , -0.0362)
QTcP (ms)	0.0001	0.0113	(-0.0225 , 0.0228)

Note: Individual data obtained prior to dosing on Day 1 in each period from all subjects in the PD analysis set are included in the analysis.

Mean QTcP values decreased over time after JNJ-28431754 administration and placebo. As the upper limits of the (2-sided) 90% CI for the difference in mean QTcP changes from baseline between JNJ-28431754 and placebo were less than 10 ms at each timepoint and for each dose of JNJ-28431754, establishing the noninferiority of the effect of JNJ 28431754 (300 mg and 1,200 mg) on QTc to that of placebo.

Summary of Pairwise Comparisons Between JNJ-28431754 (300 mg, 1,200 mg) and Placebo Based on Mixed-Effects Analysis of Variance on QTc Change From Baseline – Study Specific Power Correction (Study JNJ-28431754DIA1010: Pharmacodynamic Analysis Set)

	Pairwise Comparison JNJ-28431754 300 mg Minus ---------- Placebo ----------			Pairwise Comparison JNJ-28431754 1,200 mg Minus ---------- Placebo ----------		
	L.S. Mean[a]	SE	90 % CI	L.S. Mean[a]	SE	90 % CI
QTcP (ms)						
30 min	-2.4	1.25	(-4.48; -0.38)	-1.3	1.26	(-3.34; 0.80)
1 H	-0.6	1.25	(-2.61; 1.50)	-2.8	1.26	(-4.83; -0.69)
1 H 30 min	0.1	1.25	(-1.95; 2.15)	-1.9	1.26	(-3.99; 0.15)
2 H	-1.0	1.25	(-3.01; 1.09)	-3.9	1.26	(-5.95; -1.81)
3 H	0.5	1.25	(-1.55; 2.56)	-3.0	1.26	(-5.08; -0.94)
4 H	-0.7	1.25	(-2.77; 1.33)	-3.2	1.26	(-5.28; -1.14)
5 H	-2.0	1.25	(-4.06; 0.04)	-2.3	1.26	(-4.33; -0.19)
6 H	-1.1	1.25	(-3.16; 0.96)	-1.6	1.26	(-3.66; 0.48)
8 H	0.3	1.25	(-1.76; 2.36)	-2.5	1.26	(-4.57; -0.43)
12 H	-0.9	1.25	(-2.97; 1.14)	-3.2	1.26	(-5.26; -1.12)
24 H	0.3	1.25	(-1.74; 2.38)	-0.7	1.26	(-2.80; 1.34)

[a] L.S. Mean is difference (ΔΔQTcP) in least-square means between JNJ-28431754 and placebo in QTc change from baseline at each timepoint.

Note 1: At each scheduled timepoint, the average of the triplicate ECG reading was used for analysis.

Note 2: QTc change from baseline was analyzed using a mixed effects analysis of variance (ANOVA) model, with sequence, period, treatment, timepoint and treatment by timepoint interaction as fixed factor effects and subject as a random effect.

Mean QTcP values increased over time after moxifloxacin administration. At each timepoint, the mean QTcP change from baseline was higher for moxifloxacin compared to placebo with the (L.S.) mean difference exceeding 10 ms between 1 hour and 4 hours postdose. The lower-limit of the 2-sided 97.5% CI for the difference in mean QTcP change from baseline between moxifloxacin 400 mg and placebo exceeded 5 ms at at least 1 (selected) timepoint (1.5, 2, 3, and 4 hours postdose), establishing assay sensitivity, per the prespecified criteria.

Summary of Pairwise Comparisons Between Moxifloxacin and Placebo Based on Mixed Effects Analysis of Variance on QTc Change From Baseline - Study Specific Power Correction
(Study JNJ-28431754DIA1010: Pharmacodynamic Analysis Set)

	Pairwise Comparison ---------- Moxifloxacin 400 mg Minus Placebo ----------		
	L.S. Mean[a]	SE	97.5% CI
QTcP (ms)			
30 min	3.5	1.24	
1 H	10.4	1.24	
1 H 30 min	10.6	1.24	(7.84; 13.41)
2 H	10.2	1.24	(7.40; 12.96)
3 H	12.2	1.24	(9.45; 15.01)
4 H	12.0	1.24	(9.17; 14.73)
5 H	9.3	1.24	
6 H	9.9	1.24	
8 H	9.2	1.24	
12 H	6.0	1.24	
24 H	6.4	1.24	

[a] L.S. Mean is difference (ΔΔQTcP) in least-square means between moxifloxacin and placebo in QTc change from baseline at each timepoint.

Note 1: At each scheduled timepoint, the average of the triplicate ECG reading was used for analysis.

Note 2: QTc change from baseline was analyzed using a mixed effects ANOVA model, with sequence, period, treatment, timepoint and treatment by timepoint interaction as fixed factor effects and subject as a random effect.

Note 3: Two-sided 97.5% CI were calculated at 4 preselected timepoints (1.5, 2, 3 and 4 hours) postdosing for the statistical evaluation to establish assay sensitivity

There were no post-baseline QTcP values >500 ms or changes from baseline QTcP values >60 ms and noteworthy changes from baseline or in the incidence of values above or below the normal range in heart rate, PR intervals, or QRS intervals after treatment after either dose of JNJ-28431754. In addition, there was no increase in treatment-emergent T-wave, U-wave or other morphologic ECG abnormalities after either dose of JNJ-28431754 (300 mg or 1,200 mg).

Pharmacokinetic/Pharmacodynamic

There was no clinically meaningful relationship between the plasma concentration of JNJ-28431754 and QTc change from baseline (ΔΔQTcP).

At mean C_{max} values, predicted mean QTcP values were decreased from baseline compared to placebo. The predicted mean ΔΔQTcP with 90% CI equaled -1.3 [-1.89; -0.69] for 300 mg and -3.4 [-5.02; -1.84] for 1,200 mg.

Predicted Mean Difference in QTc Change From Baseline Between JNJ-28431754 (300 mg, 1,200 mg) and Placebo With Associated 90% CI at Mean Cmax of JNJ-28431754
(Study JNJ-28431754DIA1010: Pharmacodynamic Analysis Set)

	JNJ-28431754 300 mg Minus -------- Placebo --------			JNJ-28431754 1,200 mg Minus --------- Placebo --------		
	L.S. Mean[a]	SE	90 % CI[b]	L.S. Mean[a]	SE	90 % CI[b]
Parameter						
QTcB	-0.2	0.37	(-0.80; 0.44)	-0.5	0.98	(-2.14; 1.17)
QTcF	-1.0	0.30	(-1.54; -0.53)	-2.8	0.80	(-4.10; -1.41)
QTcP	-1.3	0.36	(-1.89; -0.69)	-3.4	0.95	(-5.02; -1.84)

[a] L.S. mean is least square mean difference between JNJ-28431754 and placebo in QTc change from baseline at mean C_{max} of JNJ-28431754.

[b] Model: Difference in QTc change from baseline (JNJ-28431754 - placebo) versus plasma concentration (ug/mL) (no fixed intercept) and a random intercept, random slope effect

PHARMACOGENOMIC RESULTS: No subject withdrew consent for pharmacogenomic research, and no genes were genotyped in this study.

SAFETY RESULTS: Twenty (33%) of the subjects receiving at least 1 dose of study medication had 1 or more treatment-emergent adverse events (TEAE, defined as adverse events starting after the first study drug administration in a given period (through the end of the wash out period) and occurring prior to the first dose administration in the next period or up to and including the post study follow up contact). Treatment-emergent adverse events occurred at similar incidences after each therapy (5 subjects [8.6%] with placebo, 7 subjects [12.3%] with the 300 mg dose, 8 subjects [14.3%] with the 1,200 mg dose, and 7 subjects [12.1%] with moxifloxacin. The most common TEAE included headache (9 subjects, 15.0%), nausea (8 subjects, 13.3%) and vomiting (5 subjects, 8.3%). No deaths, other serious adverse events, severe adverse events or hypoglycemic episodes were reported. Three subjects discontinued due to adverse events, 2 of which (myalgia and increased CPK) were reported after treatment with the 300 mg dose and 1 of which (dysuria) was reported after placebo. There were no clinically relevant changes in laboratory or vital sign parameters. The incidence of treatment-emergent rhythm abnormalities reported by subjects in the PD analysis set with both doses of JNJ-28431754 (300 mg and 1,200 mg) was comparable to placebo.

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

CONCLUSIONS:

- The systemic exposure (C_{max} and AUC_{24}) of JNJ-28431754 increases with increasing dose. For a 4-fold increase in dose, the arithmetic mean C_{max} and AUC_{24} increased by approximately 3-fold.
- At therapeutic (300 mg) and supratherapeutic (1,200 mg) doses, JNJ-28431754 does not lead to QT/QTc prolongation (QTcP above 500 ms) or changes from baseline (above 60 ms), or serious cardiovascular adverse events suggestive of an arrhythmia.
- Treatment with therapeutic (300 mg) and supratherapeutic (1,200 mg) doses of JNJ-28431754 does not lead to clinically meaningful changes in mean changes from baseline or the incidence of values out of the normal range (above or below) in heart rate, PR intervals or QRS intervals.
- Treatment with therapeutic (300 mg) and supratherapeutic (1,200 mg) doses of JNJ-28431754 does not lead to treatment-emergent rhythm, conduction or other morphologic ECG waveform abnormalities.
- Assay sensitivity was established using moxifloxacin as a positive control.
- There was no clinically meaningful relationship between the plasma concentration of JNJ-28431754 and QTc change from baseline ($\Delta\Delta$QTcP).
- Treatment with JNJ-2843175 is not associated with an increased incidence of adverse events potentially associated with QT/QTc prolongation and the proarrhythmic potential of investigational agents based on the ICH E14 Guideline (2005).
- JNJ-28431754 is safe and well tolerated when administered to healthy adults.

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