Janssen Research & Development

Synopsis
[Protocol R092670-PSY-3008; Phase 3]

JNJ-16977831-AAA (Paliperidone)

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SYNOPSIS

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Name of Sponsor/Company	Xian-Janssen Pharmaceutical Ltd
Name of Finished Product	Paliperidone palmitate
Name of Active Ingredient(s)	Paliperidone

Protocol No.: R092670-PSY-3008

Title of Study: A Randomized, Open-Label, Parallel-Group Comparative Study of Paliperidone Palmitate (50, 100, or 150 mg eq.) and Risperidone Long Acting Injection (25, 37.5, or 50 mg) in Subjects With Schizophrenia

Study Name: None.

Coordinating Investigator: [redacted] M.D. - [redacted] China

Publication (Reference): None.

Study Period: 06 January 2008 to 14 January 2009

Phase of Development: Phase 3

Objectives: The primary objective of this study was to demonstrate that paliperidone palmitate and RISPERDAL® CONSTA® (risperidone long acting injection [LAI]) have comparable efficacy. The safety and tolerability of paliperidone palmitate were also assessed. Secondary objectives included assessment of the global improvement in severity of illness associated with the use of paliperidone palmitate compared with RISPERDAL CONSTA, assessment of the benefits to personal and social functioning associated with the use of paliperidone palmitate compared with RISPERDAL CONSTA, and exploring the effects of paliperidone palmitate compared with RISPERDAL CONSTA in improvement of sleep quality and reduction of daytime drowsiness.

Methods: This was a randomized, open-label, rater-blinded, active-controlled, parallel-group, multicenter comparative study in men and women, aged 18 years or older, who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for acute schizophrenia for at least 1 year, with Positive and Negative Syndrome Scale (PANSS) total score of 60 to 120 at screening and baseline. The study comprised a screening period of no more than 7 days and a 13-week open-label treatment period. The screening period included washout of psychotropic medications and, if necessary, an oral tolerability test. For subjects without source documentation of tolerability to oral risperidone or paliperidone extended-release (ER), or injectable RISPERDAL CONSTA or paliperidone palmitate, 4 to 6 days of paliperidone ER treatment at a dosage of 6 mg/day was administered to test tolerability. This tolerability test was completed before the first administration of study drug.

In the open-label treatment period, subjects were randomly assigned in a 1:1 ratio to 1 of 2 treatment groups. In one treatment group, paliperidone palmitate was administered using a dosing regimen that included an initial intramuscular (i.m.) deltoid injection of paliperidone palmitate 150 milligram equivalent (mg eq.) at baseline, a second deltoid injection of paliperidone palmitate 100 mg eq. on Day 8, and subsequent injections of paliperidone palmitate (deltoid or gluteal) every 4 weeks, on Day 36 and Day 64. In the other treatment group, RISPERDAL CONSTA was administered every 2 weeks and oral risperidone (1 to 6 mg/day) was administered for the first 4 weeks (28 days) of the open-label treatment period. All subjects in the RISPERDAL CONSTA arm received supplementation with oral risperidone at the initiation of treatment, and with an increase in dose of RISPERDAL CONSTA on Day 36 and Day 64. If on Day 36 or Day 64, the investigator chose to increase the dose, then the subject was to be dispensed oral risperidone supplementation in the dose of 1 to 2 mg daily for 21 days. Doses could be increased or decreased for efficacy or tolerability at the discretion of the investigator.

Number of Subjects (planned and analyzed): Approximately 420 men and women were planned to be enrolled, 452 subjects were enrolled and 350 subjects completed the study.

Diagnosis and Main Criteria for Inclusion: Subjects included in the study were aged 18 years or older and met DSM-IV criteria for acute schizophrenia for at least 1 year with PANSS total score of 60 to 120 (inclusive).

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone palmitate 50 mg eq. (Batch No. 7EB5V_1), 100 mg eq. (Batch No. 7EB5X_1), and 150 mg eq. (Batch No. 7FB5B_1) injections were given i.m. at deltoid or gluteal sites. RISPERDAL CONSTA 25 mg (Batch No. 164-3714BC), 37.5 mg (Batch No. 164-3714BB), and 50 mg (Batch No. 164-3714BA) depot microsphere injections were given i.m. at a gluteal site. Paliperidone ER 3-mg tablets (Batch No. 707704) and risperidone 1-mg tablets (Batch No. 07I18/F005) were administered orally.

Duration of Treatment: The approximate length of the study for each subject was 14 weeks, including a screening period of no more than 7 days and a 13-week open-label treatment period.

Criteria for Evaluation: Efficacy assessments included PANSS, Clinical Global Impression-Severity (CGI-S), personal and social performance (PSP), and Sleep Visual Analog Scale (VAS). Safety was monitored by the evaluation of adverse events, extrapyramidal symptom (EPS) rating scales (Simpson-Angus Scale [SAS], Barnes Akathisia Rating Scale [BARS], and Abnormal Involuntary Movement Scale [AIMS]), clinical laboratory test results; vital sign measurements; electrocardiograms (ECGs); and physical examination findings. To assess the tolerability of injections, the investigators evaluated injection sites for swelling, redness, pain, and induration, and the subject assessed injection site pain.

Statistical Methods:

Efficacy: The primary endpoint was the change in the PANSS total score from baseline to the last post-randomization assessment in the open-label treatment period. The primary population for the efficacy analyses was the Per-Protocol Analysis Set, which consisted of randomly assigned subjects who i) had received at least 2 injections of the open-label medication (including the loading dose) and for whom the time between any 2 injections during the open-label treatment period did not exceed 35 days (paliperidone palmitate) or 21 days (RISPERDAL CONSTA); ii) had both the baseline measurement and at least 1 post-randomization measurement on the primary efficacy variable; iii) had a minimum exposure of 5 weeks to the open-label treatment regimen; and iv) did not have major protocol violations such as violations of entry criteria, errors in treatment assignment, and use of excluded medication. The change from the baseline score at each visit and at end point (for both last observation-carried-forward [LOCF] and observed case data) was analyzed using an analysis of covariance (ANCOVA) model with treatment as a factor and baseline PANSS total score as the covariate. The point estimate and 2-sided 95% confidence interval (CI) based on ANCOVA were provided for the difference between RISPERDAL CONSTA and paliperidone palmitate in the change in PANSS total score. Noninferiority of paliperidone palmitate to RISPERDAL CONSTA was to be concluded if the lower limit of the 2-sided 95% CI exceeded -5.5. The noninferiority analyses on the PANSS total score were provided for the intent-to-treat (ITT) Analysis Set to evaluate the consistency of results.

Secondary analyses included ANCOVA with treatment as factor and baseline score as a covariate for the change from baseline in CGI-S, PSP, sleep VAS, and PANSS subscales. For the responder rate, the point estimate and 2-sided 95% CI for the relative risk were provided using a Mantel-Haenszel test.

Safety: Safety analyses included summaries of the percentage of subjects with treatment-emergent adverse events; descriptive statistics for changes in clinical laboratory test results, ECG parameters (including PR, QRS, QT, and QTc intervals), vital signs, weight, waist circumference, and body mass index (BMI); a frequency table for orthostatic hypotension; summaries of EPS scales (SAS, BARS, and AIMS); and summaries of injection site evaluations.

RESULTS:

The completion rate was 72.1% for the paliperidone palmitate group and 83.0% for the RISPERDAL CONSTA group. More subjects in the paliperidone palmitate group (9.6%) were withdrawn due to lack of efficacy than in the

RISPERDAL CONSTA group (4.0%). Most subjects in the Per-Protocol Analysis Set received all injections (84.4% in the paliperidone palmitate group, and 90.4% in the RISPERDAL CONSTA group).

The 2 treatment groups were well matched in demographic and baseline disease characteristics. More female subjects (60.0%) were enrolled. All except 1 subject were of Han ethnicity. The mean age was 31.7 years. The mean BMI was 23.1 kg/m^2, and approximately 5% of the subjects were obese (BMI≥30 kg/m^2) at baseline. Most subjects had a primary diagnosis of paranoid schizophrenia (66.6%). The mean PANSS total score at baseline was 83.2.

EFFICACY RESULTS:

Primary Efficacy Analysis: The mean change from baseline to end point (LOCF) in PANSS total score in the Per-Protocol Analysis Set was -23.6 in the paliperidone palmitate group and -26.9 in the RISPERDAL CONSTA group. Based on ANCOVA, the difference between RISPERDAL CONSTA and paliperidone palmitate in least-squares (LS) means was -2.3 with a 95% CI of (-5.20, 0.63). Since the lower limit of the 95% CI was greater than the predetermined noninferiority margin of -5.5, paliperidone palmitate was demonstrated to be noninferior to RISPERDAL CONSTA in the primary analysis set (Per-Protocol).

PANSS Total Score - Change from Baseline to End Point (LOCF)
(Study R092670-PSY-3008:Per-Protocol Analysis Set)

	R092670 (N=205)	RISPERDAL CONSTA (N=208)
Baseline		
N	205	208
Mean (SD)	82.1(11.95)	84.4(12.69)
Median (Range)	79.0(59;115)	83.0(60;120)
End point		
N	205	208
Mean (SD)	58.5(16.77)	57.5(16.38)
Median (Range)	55.0(30;118)	54.0(31;106)
Change from Baseline		
N	205	208
Mean (SD)	-23.6(16.28)	-26.9(15.43)
Median (Range)	-23.0(-70; 27)	-27.0(-70; 19)
Diff. of LS Means (SE)[a,b]		-2.3(1.48)
95% CI		(-5.20;0.63)

[a] Based on ANCOVA model with treatment as a factor, and baseline value as a covariate.
[b] RISPERDAL CONSTA - R092670.
Note: Negative change in score indicates improvement.

In the ITT Analysis Set, the difference between RISPERDAL CONSTA and paliperidone palmitate in LS means for the change in PANSS total score was -4.0 with a 95% CI of (-7.13, -0.89).

Other Efficacy Results: Improvement in CGI-S, PSP, sleep quality, daytime drowsiness, and the 5 Marder factors of PANSS was seen with similar magnitudes of change in the 2 treatment groups. Based on ANCOVA, the 2-sided 95% CIs between the 2 treatment groups included 0 for all these secondary efficacy variables in the Per-Protocol Analysis Set, with the exception of the positive symptom subscale of PANSS, for which the difference in LS means between RISPERDAL CONSTA and paliperidone palmitate was small and not clinically significant. The 2-sided 95% CIs for the relative risk of paliperidone palmitate vs. RISPERDAL CONSTA for subjects who improved from baseline by ≥20%, ⩾30%, or ⩾50% in PANSS total score at the end of the study in the Per-Protocol Analysis Set all included 1. Results of secondary efficacy analysis support the comparable efficacy of paliperidone palmitate to RISPERDAL CONSTA.

SAFETY RESULTS: Paliperidone palmitate i.m. injections dosed between 50 and 150 mg eq. on Days 1, 8, 36, and 64 were generally well tolerated by adult subjects with schizophrenia. The safety profile of paliperidone palmitate was comparable to that of RISPERDAL CONSTA i.m. injections dosed between 25 and 50 mg on Days 8, 22, 36,

50, 64, and 78 with oral risperidone supplementation. The safety and tolerability results in this study were generally consistent with previous clinical studies of paliperidone palmitate.

The overall summary of treatment-emergent adverse events is presented below.

Overall Summary of Treatment-Emergent Adverse Events
(Study R092670-PSY-3008: Safety Analysis Set)

	R092670 (N=229) n(%)	RISPERDAL CONSTA (N=223) n(%)	Total (N=452) n(%)
TEAE	168 (73.4)	167 (74.9)	335 (74.1)
Possibly related TEAE[a]	139 (60.7)	145 (65.0)	284 (62.8)
1 or more serious TEAE	3 (1.3)	8 (3.6)	11 (2.4)
TEAE leading to permanent stop	8 (3.5)	9 (4.0)	17 (3.8)
TEAE leading to death	0	1 (0.4)	1 (0.2)

[a] Study drug relationships of possible, probable, and very likely based on assessment of investigator are included in this category.

The most common treatment-emergent adverse events reported were akathisia, tremor, and insomnia in both treatment groups. The incidences of serious adverse events and adverse events leading to study discontinuation were ≤4% in each treatment group, and none of these event was reported in more than 2 subjects in either treatment group. Most EPS-related adverse events were mild or moderate in severity. Increases in prolactin level were observed in both treatment groups, and the majority of potentially prolactin-related adverse events were blood prolactin increased without reported clinical symptoms. There were no clinically significant changes in the overall EPS rating scales, clinical laboratory, vital signs, or ECG measurements. There were small increases in mean body weight (1.5 kg) and BMI (0.6 kg/m^2) from baseline to the end of the study for each treatment group. Local injection site tolerability was good.

STUDY LIMITATIONS: In this open-label study, both study personnel (except efficacy raters) and the subjects knew the treatment assignment. Since RISPERDAL CONSTA and the risperidone tablet are known to be efficacious in the treatment of schizophrenia, while paliperidone palmitate was the experimental medication in this study, the expected outcome for the 2 treatments may have been biased. This may explain the higher withdrawal rate in the paliperidone palmitate group.

CONCLUSION: Open-label treatment with paliperidone palmitate i.m injection at flexible doses between 50 and 150 mg eq. was as effective as RISPERDAL CONSTA at flexible doses between 25 and 50 mg with oral risperidone supplementation in the treatment of schizophrenia in adult subjects as measured by the primary efficacy endpoint. Paliperidone palmitate i.m. injections were generally safe and well tolerated, and no new safety signals were detected.