SYNOPSIS

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Name of Sponsor/Company	Ortho-McNeil Janssen Scientific Affairs, L.L.C.
Name of Finished Product	Paliperidone ER
Name of Active Ingredient(s)	(+)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyridol[1,2-a]pyrimidin-4-one

Protocol No.: R076477-SCA-3001 CR010498

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Study to Evaluate the Efficacy and Safety of Two Dosages of Paliperidone ER in the Treatment of Subjects with Schizoaffective Disorder

Coordinating Investigator: Joseph Kwentus, M.D. , Precise Research Center, Flowood, MS, USA

Publication (Reference): none

Study Period: 31 October 2006 to 21 February 2008. Database lock: 14 April 2008.

Phase of Development: Phase 3

Objectives:

Primary objective:

- The primary objective of this study was to evaluate the efficacy of 2 dose groups of paliperidone ER, low dose (6 mg/day with option to reduce to 3 mg/day), and high dose (12 mg/day with option to reduce to 9 mg/day), compared with placebo in the treatment of acutely ill subjects with schizoaffective disorder as measured by the Positive and Negative Syndrome Scale (PANSS) total score. The safety and tolerability of paliperidone ER in subjects with schizoaffective disorder was also assessed.

Secondary objectives:

- Assessment of the rate of response to paliperidone ER among subjects with schizoaffective disorder. Response was defined as a ≥30% reduction from baseline in the PANSS total score and a Clinical Global Impression of Change for Schizoaffective Disorder (CGI-C-SCA) ≤2.
- Evaluation of the effects of paliperidone ER on mood symptoms in subjects with schizoaffective disorder, as measured by relevant PANSS factor scores (hostility/excitement and depression/anxiety).

Methods: Study R076477-SCA-3001 was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. The study included a screening and washout period followed by randomization and double-blind treatment for 6 weeks. Subjects with an established diagnosis of schizoaffective disorder who were experiencing acute exacerbation of the illness were randomly assigned in a 1:1:1 ratio to receive oral treatment with paliperidone ER low dose, paliperidone ER high dose, or placebo. Paliperidone ER was initiated at a dose of 6 mg/day (low dosage) or 12 mg/day (high dosage). Dosages could be reduced at any time up to the Day 15 visit to 3 mg/day and 9 mg/day, respectively, if tolerability issues arose. Following dosage reduction, subjects must have remained on the reduced dosage for at least 4 days. After that, 1 additional dosage adjustment back to the initial dose level was allowed if clinically indicated. No further dosage adjustments were allowed following the Day 15 visit. After the screening visit, all eligible and enrolled subjects were hospitalized until at

least Day 8. Subjects could be discharged after their Day 8 assessments had been completed, providing that based on the investigator's clinical judgment, they were considered appropriate for outpatient care, their condition was expected to remain stable or improve with regular outpatient follow-up, and they were not considered at risk for suicide or violent behavior.

Number of Subjects (planned and analyzed): Randomization of 315 subjects (105 per group) was planned. A total of 316 subjects were randomized and 310 were included in the ITT analysis set.

Diagnosis and Main Criteria for Inclusion: Subjects were men and women between 18 and 65 years, inclusive, with acute exacerbation of symptoms who met DSM-IV criteria for schizoaffective disorder (295.70), as confirmed by the Structured Clinical Interview for DSM-IV Disorders (SCID). The subjects must have had a PANSS total score of at least 60 and a score of ≥4 on at least 2 of the following PANSS items: Hostility (P7), Excitement (P4), Tension (G4), Uncooperativeness (G8), and Poor Impulse Control (G14). In addition, subjects must have had prominent mood symptoms, with a score of ≥16 on the Young Mania Rating Scale (YMRS) and/or on the Hamilton Rating Scale for Depression (HAM-D-21) and met all other inclusion and none of the exclusion criteria in order to participate in this study. Subjects receiving treatment with antidepressants and/or mood stabilizers were permitted, provided these medications had been given at a generally stable dose within 30 days of screening.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER 6 mg tablets for oral use, batch nos. 348346/05H01/F061, 348347/05H01/F061, 348349/05H01/F061, 348432/06D24/F061. Paliperidone ER 3 mg tablets for oral use, batch nos. 348345/05E23/F022, 348346/05E23/F022, 348432/06C03/F022.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo tablets for oral use, batch nos. 348345/06B21/F027, 348348/06B21/F027, 348349/06B21/F027, 348432/06F27/F027.

Duration of Treatment: 43 Days

Criteria for Evaluation:

Efficacy: The primary efficacy outcome was the change from baseline to Week 6, or the last post-randomization assessment (LOCF end point) in the double-blind phase, in the PANSS total score.

Secondary efficacy outcomes included:

- Change from baseline to Week 6 LOCF end point in Clinical Global Impression of Severity for Schizoaffective Disorder (CGI-S-SCA) score and CGI-C-SCA ratings at Week 6 LOCF end point as compared with baseline
- Change from baseline to Week 6 LOCF end point in PANSS subscales and factor scores
- Responder rates, with response being defined as a ≥30% improvement from baseline to endpoint in PANSS total score and CGI-C-SCA ≤2 (much improved or very much improved) at Week 6 LOCF end point.
- Time to first response

Other outcomes included the change from baseline to Week 6 LOCF end point in the YMRS and HAM-D-21 scores.

Safety: Safety assessments included AEs, clinical laboratory testing (hematology; fasting serum chemistry, including fasting lipids and prolactin levels; and urinalysis), pregnancy testing, vital signs measurements (respiratory rate, blood pressure, pulse, temperature, weight), physical examination, a 12-lead ECG, movement disorders side effect scales (AIMS, BARS, and SAS), and the ISST.

Pharmacogenomics: Approximately 10 mL of whole blood was obtained for genetic analysis from subjects who provided specific written informed consent to participate in the genetics portion of the study. No genetic analysis had been performed when this report was written.

Statistical Methods: There were 2 analysis sets used in analyses: Intent-to-treat (ITT) analysis set for efficacy analyses and safety analysis set for all safety analyses.

The ITT analysis set was defined as all subjects who were randomized to treatment group and received at least 1 dose of study medication (or any portion of a dose) and had both baseline and at least 1 postbaseline PANSS assessment.

The safety analysis set included all subjects who received at least 1 dose of study medication (or any portion of a dose), regardless of their compliance with the protocol, and regardless of whether they received study medication that was different from the medication to which they were randomly assigned.

The primary efficacy variable was the change in the PANSS total score from baseline to Week 6 LOCF end point. This variable was analyzed using an ANCOVA. The model included treatment, stratum (treatment with concomitant medications [antidepressants and/or mood stabilizers] vs. no treatment with such concomitant medications), and country, as fixed effect design factors, and baseline PANSS total score as a covariate. The 2 primary pairwise comparisons were paliperidone ER low dose vs. placebo and paliperidone ER high dose vs. placebo. The Hochberg step-up procedure was used to address multiplicity.

The secondary efficacy variables included changes from baseline to Week 6 LOCF end point in the selected PANSS factor scores. These changes were analyzed using the same method as the primary efficacy analysis (with the covariate in the ANCOVA model being the baseline value of the respective variable). In addition, CGI-S-SCA was analyzed using an ANCOVA model with the same factors as the primary efficacy analysis. The CGI-C-SCA analysis was based on the ANOVA without the covariate baseline score in the model.

Responders were defined as subjects with a ≥30% improvement from baseline to Week 6 LOCF end point in PANSS total score and CGI-C-SCA ≤2 at the Week 6 LOCF end point. Response incidence was analyzed using the Cochran-Mantel-Haenszel test and time to event analysis.

Changes in YMRS and HAM-D-21 were also analyzed, using the same method as the primary efficacy analysis (with the covariate in the ANCOVA model being the baseline value of the respective variable).

RESULTS:

Eligible subjects (n=316) were randomly assigned in a 1:1:1 ratio to receive low dose (6 mg/day) paliperidone ER (n=109), high dose (12 mg/day) paliperidone ER (n=100), or placebo (n=107). The 316 randomized subjects were assigned to treatment groups using stratified randomization, where the strata were: treatment with antidepressants and/or mood stabilizers (concomitant medication stratum) or no treatment with antidepressants and/or mood stabilizers (no concomitant medication stratum). Across treatment groups, 38.3% of subjects were treated with concomitant antidepressants and/or mood stabilizers, while 61.7% were not treated with concomitant antidepressants and/or mood stabilizers.

The majority of the ITT analysis set (n=310) was male (64.8%) and 46.5% of the subjects were Caucasian. The mean age was 37.3 years, ranging from 18 to 61 years. The baseline PANSS mean (SD) score ranged from 91.6 – 95.9. Overall, 64.7% and 82.8% of subjects had a baseline score ≥16 on the HAM-D-21 and YMRS, respectively; 47.6% of subjects met this criterion on both scales.

Of the 316 randomized subjects, 212 (67.1%) subjects completed double-blind treatment. The highest completion rate was observed in the paliperidone ER high dose group (77.0%), and the lowest completion rate was observed in the placebo group (58.9%). A higher percentage of subjects in the placebo group (20.6%) discontinued due to lack of efficacy than in any other treatment group (paliperidone ER low dose group: 11.0%, and paliperidone ER high dose group: 9.0%).

EFFICACY RESULTS:

The results of the primary efficacy variable (change from baseline to Week 6 LOCF end point in PANSS total score) demonstrated the efficacy of the paliperidone ER high dose. There were decreases in the PANSS total score in all treatment groups, indicating improvement in the severity of neuropsychiatric symptoms. The mean (SD) change from baseline to endpoint in PANSS total score was -21.7 (21.4) in the placebo group, -27.4 (22.1) in the paliperidone ER low dose group, and -30.6 (19.1) in the paliperidone ER high dose group. The difference from placebo was statistically significant for the paliperidone ER high dose group ($p=0.003$) but not for the paliperidone ER low dose group.

The proportion of subjects who responded to treatment (30% or more improvement in PANSS total score and a CGI-C-SCA score of ≤ 2) was significantly greater in the both the paliperidone ER low dose ($p=0.008$) and high dose ($p=0.001$) groups compared with the placebo group at Week 6 LOCF end point. The responder rate was 40.2% in the placebo group, 56.7% in low dose paliperidone ER group, and 62.2% in the high dose paliperidone ER group. There was a statistically significant difference in the time to first composite response between the paliperidone ER high dose group and the placebo group ($p=0.026$).

Additional predefined secondary efficacy parameters included PANSS subscale and factor scores, CGI-S-SCA and CGI-C-SCA, YMRS, and HAM-D-21. At Week 6 LOCF end point, the paliperidone ER high dose group was significantly superior ($p\leq 0.05$) to placebo in reduction from baseline 2 of 3 PANSS sub-scales (Positive and General Psychopathology), reduction from baseline in 3 of the 5 PANSS factor scores (Positive, Disorganized Thought, and Uncontrolled Hostility/Excitement), reduction from baseline in CGI-S-SCA total score, and 3 of the 4 CGI-S-SCA domain scores (Positive, Negative, and Manic), improvement from baseline in CGI-C-SCA overall score, and reduction in HAM-D-21 and YMRS score total scores in subjects with a baseline HAM-D-21 total score ≥ 16.

While paliperidone ER low dose did not separate from placebo on the primary efficacy parameter, paliperidone ER low dose was significantly superior ($p\leq 0.05$) to placebo in responder rates, in improvement from baseline in CGI-C-SCA overall score, and in reduction in HAM-D-21 total score in subjects with a baseline HAM-D-21 total score ≥ 16.

Across treatment groups, reduction in PANSS total score correlated highly with reduction in HAM-D-21 total score and YMRS total score.

Week 6 LOCF **Change from Baseline** Mean Change (SD)	Placebo (N=107)	PALI ER Low Dose (N=105)	PALI ER High Dose (N=98)
PANSS Total Score (primary variable)	-21.7 (21.4)	-27.4 (22.1)	-30.6 (19.1)**
PANSS Subscale Scores			
Positive Subscale Score	-7.9 (6.6)	-9.1 (7.1)	-11.3 (6.3)**
Negative Subscale Score	-3.1 (5.1)	-4.4 (5.6)	-4.2 (5.1)
General Psychopathology Subscale Score	-10.7 (11.6)	-13.9 (12.0)	-15.1 (10.3)**
PANSS Factor Scores			
Positive Factor Score	-6.7 (6.9)	-8.0 (6.8)	-9.6 (6.4)**
Negative Factor Score	-3.0 (5.0)	-4.5 (5.7)	-4.0 (5.1)
Disorganized Thought Factor Score	-3.7 (5.2)	-5.0 (5.0)	-5.7 (4.8)**
Uncontrolled Hostility/Excitement Factor Score	-4.8 (4.4)	-5.4 (4.8)	-7.0 (4.2)**
Anxiety/Depression Factor Score	-3.4 (4.0)	-4.5 (3.8)	-4.3 (3.7)
CGI-S-SCA			
Overall Score	-1.1 (1.3)	-1.4 (1.2)	-1.8 (1.0)**
Positive Domain Score	-1.3 (1.3)	-1.5 (1.3)	-1.9 (1.2)**
Negative Domain Score	-0.5 (0.9)	-0.7 (1.0)	-0.8 (1.1)*
Depressive Domain Score	-0.7 (1.3)	-1.0 (1.6)	-0.9 (1.3)
Manic Domain Score	-0.9 (1.4)	-1.1 (1.5)	-1.6 (1.4)**
CGI-C-SCA (n)	107	104	98
Overall Score	2.9 (1.4)	2.6 (1.3)*	2.2 (1.1)**
HAM-D-21 (n)	64	75	61
Total Score	-9.9 (10.7)	-13.6 (9.2)*	-14.5 (9.2)*
YMRS (n)	90	88	79
Total Score	-11.5 (11.4)	-14.3 (11.8)	-19.4 (11.7)**
Responder Rate (n)	107	104	98
30% Decrease in PANSS Total Score and CGI-C-SCA ≤2	43 (40.2%)	59 (56.7%)**	61 (62.2%)**

* Denotes a statistically significant ($p<0.05$) improvement in score vs. placebo, ** Denotes significant improvement at the 0.01 alpha level.

Note: Baseline is defined as the last measurement prior to the first dose of study medication. LOCF time points (Day 4 and Weeks 1-6) are defined as the last non-missing, postbaseline measurement carried forward to that visit.

SAFETY RESULTS:

Overall Summary of Treatment-Emergent Adverse Events During Double-Blind Phase
(Study R076477-SCA-3001:Safety Analysis Set)

	Placebo (N=107) n (%)	PALI ER Low Dose (N=108) n (%)	PALI ER High Dose (N=98) n (%)	Total PALI ER (N=206) n (%)
TEAE	61 (57.0)	78 (72.2)	68 (69.4)	146 (70.9)
Possibly related TEAE (a)	40 (37.4)	54 (50.0)	50 (51.0)	104 (50.5)
TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1 or more serious TEAE	6 (5.6)	10 (9.3)	2 (2.0)	12 (5.8)
TEAE leading to treatment discontinuation	8 (7.5)	10 (9.3)	3 (3.1)	13 (6.3)

(a) Study drug relationships of possible, probable, and very likely are included in this category.

The overall incidence of TEAEs was 57.0% in placebo-treated subjects, 72.2% in paliperidone ER low dose subjects, and 69.4% in paliperidone ER high dose subjects. The most common TEAEs reported more frequently (≥3% difference) in the paliperidone ER-treated subjects than in the placebo-treated subjects were dyspepsia, hypertonia, somnolence, and tremor. Of these events, somnolence occurred more frequently in the paliperidone ER high dose group compared with the paliperidone ER low dose group. Most TEAEs were mild or moderate in severity. No subject in the paliperidone ER high dose group experienced a severe TEAE. There was a higher incidence of severe TEAEs in the paliperidone ER low dose group compared with the placebo group. The majority of severe TEAEs coded to the Psychiatric Disorders system organ class (SOC).

No subject died during the study. A higher percentage of subjects in the paliperidone ER low dose group (9.3%) experienced treatment emergent SAEs compared with subjects in the placebo (5.6%) or paliperidone ER high dose (2.0%) groups. The majority of SAEs coded to the Psychiatric Disorders SOC.

A lower percentage of subjects in the paliperidone ER high dose group (3.1%) experienced TEAEs leading to discontinuation of treatment compared with the subjects in the placebo (7.5%) and paliperidone ER low dose (9.3%) groups. The majority of TEAEs leading to treatment discontinuation coded to the Psychiatric Disorders SOC.

The frequency of TEAEs leading to dose adjustment was higher in the paliperidone ER high dose and the paliperidone ER low dose groups compared with the placebo group. TEAEs leading to dose adjustment that were reported by at least 2 subjects in either paliperidone ER group were: dystonia, hypertonia, somnolence, sedation, and tremor.

The incidence of treatment-emergent EPS-related AEs was comparable between the paliperidone ER groups and greater than that of the placebo group. Events that occurred more frequently in at least 1 of the paliperidone ER groups than in the placebo group were dystonia, drooling, hypertonia, and tremor. Of these, only dystonia had a higher incidence in the paliperidone ER high dose group compared with the paliperidone ER low dose group. Hypertonia occurred more frequently in the subjects in the paliperidone ER low dose group compared with the paliperidone ER high dose group. None of the EPS-related AEs were considered to be severe; all were mild or moderate in severity. No EPS-related event was reported as a SAE. Two EPS-related events in paliperidone ER treated subjects resulted in treatment discontinuation. The changes from baseline to Week 6 and Week 6 LOCF in EPS rating scale scores (SAS, BARS, and AIMS) were similar in the 3 treatment groups, and indicated minimal EPS related impairment.

Consistent with the known pharmacology of paliperidone, increases in prolactin levels were observed with greater frequency in subjects who received paliperidone ER, in a dose-related pattern. The low incidence of potentially prolactin-related AEs suggests that the clinical relevance of the pharmacologic effect is limited over a 6-week period.

Shifts in ALT values from normal at baseline to high at Week 6 LOCF had a higher incidence (7.0%) in the paliperidone ER high dose group compared with the placebo (no subject) and paliperidone ER low dose (2.4%) groups. Only 1 subject in the paliperidone ER high dose group had a markedly abnormal elevation in ALT. There were no subjects who met criteria for Hy's Law at any time during the study. There were no other notable treatment group differences for other liver enzymes. No subject experienced a TEAE related to liver abnormalities.

Shifts in fasting glucose values from normal at baseline to high at Week 6 LOCF had a higher incidence in the paliperidone ER low dose group (12.2%) compared with the placebo (1.3%) and paliperidone ER high dose group (3.9%). Only 1 subject in the paliperidone ER low dose group had a markedly abnormal elevation in fasting glucose at Week 6 LOCF and no subject experienced a TEAE related to glucose abnormalities during the double-blind period. One subject in the paliperidone ER low dose group had a post-treatment TEAE of blood glucose increased that the investigator considered to be secondary to a cardiac arrest.

Shifts in hemoglobin and hematocrit values from normal at baseline to low at Week 6 LOCF had a higher incidence in both paliperidone ER groups compared with the placebo group. No subject had a markedly abnormal decrease in hemoglobin or hematocrit. One subject in the paliperidone ER high dose group experienced a TEAE of anemia.

Assessment of ECG data did not reveal clinically significant QTc prolongation with paliperidone ER at doses up to 12 mg/day. No subject had a maximum postbaseline QTcLD, QTcB, or QTcF >480 msec. No subject experienced an increase of >60 msec from average predose QTc values. The incidence of subjects having a change from average predose meeting the classification of "concern" (30-60 msec) was greater in the paliperidone ER low dose group compared with the paliperidone ER high dose group and placebo group at Week 6 and Week 6 LOCF.

Over the 6-week treatment period, weight increased more in the paliperidone ER subjects compared with placebo-treated subjects. There was a greater incidence of treatment-emergent weight gain ≥7% from baseline in the paliperidone ER groups compared with the placebo group. There was a dose-related trend in the percentage of paliperidone ER subjects with treatment-emergent weight gain, which was most notable at Week 6 and Week 6 LOCF. More subjects in the paliperidone ER groups (4.1% to 4.6%) experienced TEAEs of weight increased compared with subjects in the placebo group (0.9%).

Decreases from baseline in ISST scores were seen in all 3 treatment groups at Week 6 and Week 6 LOCF, with the greatest decreases evident at Week 6. At Week 6 there was a higher percentage of subjects in the paliperidone ER high dose group with ISST ≥1 compared with the placebo and low dose paliperidone ER groups, however these differences were not seen at Week 6 LOCF.

STUDY LIMITATIONS: None.

CONCLUSION:

This study demonstrated the efficacy of paliperidone ER in subjects with an acute exacerbation of schizoaffective disorder. Superiority was consistently observed for high dose paliperidone ER compared to placebo on change from baseline in PANSS total score, several PANSS factors (positive, disorganized thought, and hostility/excitement), responder rates, and the overall CGI-S-SCA scale, as well as on the CGI-S-SCA positive, negative and manic domains. High dose paliperidone ER was also effective in reducing manic and depressive symptoms in patients with prominent affective symptomatology. While low dose paliperidone ER did not separate from placebo on the primary efficacy parameter, low dose paliperidone ER did show superiority over placebo in responder rates, in CGI-C-SCA improvement, and in reducing depressive symptoms in subjects with prominent depressive symptoms at baseline.

The overall safety findings were similar to those observed in previous studies with paliperidone ER in schizophrenia, and no new safety signal was detected. The study medication was safe and well tolerated.

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