SYNOPSIS

Issue Date: 18 November 2008
Document No.: EDMS-PSDB-9006510:2.0

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.: CR013099

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

Coordinating Investigator: David Walling, Ph.D., Collaborative Neuroscience Network Inc., Garden Grove, California; USA

Publication (Reference): none

Study Period: 08 December 2006 to 01 July 2008. Database lock: 29 July 2008.

Phase of Development: Phase 3

Objectives:

Primary objective:

- The primary objective of this study was to evaluate the efficacy of flexibly dosed paliperidone ER (3 to 12 mg/day in 3 mg/day increments), compared with placebo in the treatment of acutely ill subjects with schizoaffective disorder over 6 weeks. 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 compared with placebo on mood symptoms in subjects with schizoaffective disorder, as measured by relevant PANSS factor scores (hostility/excitement and anxiety/depression).

Methods: Study R076477-SCA-3002 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 2:1 ratio to receive oral treatment with flexibly dosed paliperidone ER (3 to 12 mg/day in 3 mg/day increments) or placebo. The randomization was stratified by site and by treatment with concomitant medications (antidepressants and/or mood stabilizers) vs. no concomitant treatment with those medications. Paliperidone ER was initiated at a dose of 6 mg/day. The study medication could be increased or decreased by 1 dose level (3 mg increment) after the Day 4 dose had been administered. Doses could be decreased by 1 level per day after the Day 8 dose had been administered and at any time thereafter until Day 15. Dose increases by 1 dose level (3 mg increment) were allowed on Day 8 and thereafter until Day 15, but at intervals no sooner than 4 doses following any previous dose adjustment. No dose adjustments were permitted after the Day 15 visit.

After the screening visit, all eligible and enrolled subjects were hospitalized until at least the Day 8 visit. The 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 300 subjects (paliperidone ER: 200 subjects; placebo: 100 subjects) was planned. A total of 311 subjects were randomized and 304 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 an acute exacerbation of symptoms who met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (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 9 mg tablets for oral use, batch nos. 349776/05126/F023, 350823/05126/F023, 353843/07F15/F068, 353844/07F15/F068, 354031/07F15/F068, 354052/07F15/F068, 354053/07F15/F068, 354054/07F15/F068.

Paliperidone ER 6 mg tablets for oral use, batch nos. 349776/06D24/F061, 350823/06D24/F061, 353843/07F08/F067, 353844/07F08/F067, 354031/07F08/F067, 354052/07F08/F067, 354053/07F08/F067, 354054/07F08/F067.

Paliperidone ER 3 mg tablets for oral use, batch nos. 349776/06C03/F022, 350823/06G03/F022, 353843/07E22/F066, 353844/07E18/F066, 354031/07E22/F066, 354052/07E22/F066, 354053/07E22/F066, 354054/07E22/F066, 354245/07E22/F066.

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

Placebo tablets for oral use, batch nos. 349776/06F28/F027, 349776/06F27/F027, 350823/06J13/F027, 353843/06J16/F027, 353844/06J16/F027, 354052/07E15/F027, 354053/07E15/F027, 354054/07E15/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 (last observation carried forward [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 end point 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 adverse events (AEs), clinical laboratory testing (hematology; fasting serum chemistry, including fasting lipids and prolactin levels; and urinalysis), pregnancy testing, vital signs measurements (respiratory rate [RR], blood pressure [BP], pulse, temperature, weight), physical examination, a 12-lead electrocardiogram (ECG), movement disorders side effect scales (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rathing Scale [BARS], and Simpson-Angus Rating Scale [SARS]), and the InterSePT Scale for Suicidal Thinking (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 randomly assigned to treatment 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 analysis of covariance (ANCOVA) model. 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 primary comparison was flexibly dosed paliperidone ER vs. placebo.

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 analysis of variance (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 for subjects with values ≥16 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=311) were randomly assigned in a 2:1 ratio to receive paliperidone ER (n=216), or placebo (n=95) and followed for 6 weeks. At the time of randomization, the 311 randomized subjects were stratified into 2 groups based on concomitant medication usage: 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, 52.1% of subjects

were treated with concomitant antidepressants and/or mood stabilizers, while 47.9% were not treated with concomitant antidepressants or mood stabilizers.

The majority of the ITT analysis set (n=304) was male (55.9%) and 51.3% of the subjects were White. The mean age was 37.6 years, ranging from 19 to 61 years. The baseline PANSS mean (SD) score was 92.1 (13.1), ranging from 91.7 to 92.3. Overall, 69.1% and 76.0% of subjects had a baseline score ≥16 on the HAM-D-21 and YMRS, respectively; 45.1% of subjects met this criterion on both scales.

Of the 311 randomized subjects, 186 (59.8%) subjects completed double-blind treatment. A higher completion rate was observed in the paliperidone ER group (62.0%) than in the placebo group (54.7%). A higher percentage of subjects in the placebo group (16.8%) discontinued due to lack of efficacy than in the paliperidone ER group (10.2%).

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 flexibly dosed paliperidone ER. There were decreases in the PANSS total score in both treatment groups, indicating improvement in the severity of neuropsychiatric symptoms. The mean (SD) change from baseline to Week 6 LOCF end point was -10.8 (18.7) in the placebo group and -20.0 (18.9) the paliperidone ER group. There was a statistically significant improvement from baseline to Week 6 LOCF end point in PANSS total score for subjects in the paliperidone ER treatment group compared with the placebo group ($p<0.001$). The decrease from baseline in PANSS total scores for the paliperidone ER treatment group was statistically significantly greater than that of the placebo group beginning at Day 4 and at every time point thereafter. No significant treatment-by-concomitant medication stratum interaction was detected at the 10% significance level.

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 ($p=0.046$) in the paliperidone ER treatment group compared with the placebo group at Week 6 LOCF end point. The responder rate was 28.0% in the placebo group and 40.5% in the paliperidone ER treatment group.

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 treatment group was significantly superior ($p\leq0.05$) to placebo for the reduction from baseline in all PANSS subscales (Positive, Negative, and General Psychopathology), the reduction from baseline in all PANSS factor scores (Positive, Negative, Disorganized Thought, Uncontrolled Hostility/Excitement, and Anxiety/Depression), the reduction from baseline in CGI-S-SCA overall score, and 3 of the 4 CGI-S-SCA domain scores (Positive, Negative, and Depressive), the CGI-C-SCA overall score, and the reduction in HAM-D-21 and YMRS total scores in subjects with baseline total scores ≥16 on the HAM-D-21 and YMRS, respectively.

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

Week 6 LOCF **Change from Baseline** Mean (SD)	Placebo (N=93)	PALI ER (N=211)
PANSS Total Score (primary variable)	-10.8 (18.7)	-20.0 (18.9)**
PANSS Subscale Scores		
Positive Subscale Score	-4.6 (6.3)	-7.3 (6.9)**
Negative Subscale Score	-1.1 (5.5)	-3.0 (4.9)**
General Psychopathology Subscale Score	-5.2 (9.4)	-9.7 (9.9)**
PANSS Factor Scores		
Positive Factor Score	-3.3 (5.8)	-6.0 (6.9)**
Negative Factor Score	-1.1 (5.7)	-3.1 (5.2)**
Disorganized Thought Factor Score	-1.4 (4.3)	-3.3 (4.5)**
Uncontrolled Hostility/Excitement Factor Score	-2.7 (4.2)	-4.3 (4.4)**
Anxiety/Depression Factor Score	-2.3 (3.6)	-3.3 (3.7)*
CGI-S-SCA		
Overall Score	-0.7 (1.2)	-1.2 (1.2)**
Positive Domain Score	-0.8 (1.2)	-1.3 (1.3)**
Negative Domain Score	-0.3 (0.9)	-0.5 (1.0)*
Depressive Domain Score	-0.4 (1.1)	-0.8 (1.3)**
Manic Domain Score	-0.6 (1.2)	-0.9 (1.3)
CGI-C-SCA[1]		
Overall Score	3.4 (1.5)	2.8 (1.3)**
HAM-D-21 (n)	65	145
Total Score	-6.2 (8.6)	-10.2 (8.7)**
YMRS (n)	70	161
Total Score	-5.7 (10.0)	-10.6 (10.8)**
Responder Rate (n)	93	210
>= 30% Decrease in PANSS Total Score and CGI-C-SCA ≤2, n (%)	26 (28.0%)	85 (40.5%)*

* 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 are defined as the last non-missing, postbaseline measurement carried forward to that visit.

[1]Note: CGI-C-SCA overall score represents the observed score at Week 6 LOCF.

SAFETY RESULTS:

Overall Summary of Treatment-Emergent Adverse Events During Double-Blind Phase
(Study R076477-SCA-3002: Safety Analysis Set)

	Placebo (N=95) n (%)	PALI ER (N=214) n (%)
TEAE	57 (60.0)	140 (65.4)
Possibly related TEAE [(a)]	30 (31.6)	99 (46.3)
TEAE leading to death	0	0
1 or more serious TEAE	8 (8.4)	11 (5.1)
TEAE leading to treatment discontinuation	8 (8.4)	11 (5.1)

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

The overall incidence of TEAEs was 65.4% in paliperidone ER subjects and 60.0% in placebo-treated subjects. The most common TEAEs reported more frequently (≥3% difference) in the paliperidone ER-treated subjects than in the placebo-treated subjects were akathisia and dizziness. Most TEAEs were mild or moderate in severity. There was a lower incidence of severe TEAEs in the paliperidone ER group compared with the placebo group. The majority of severe TEAEs coded to the Psychiatric Disorders SOC.

No subject died during the study. A lower percentage of subjects in the paliperidone ER group (5.1%) experienced treatment-emergent SAEs compared with subjects in the placebo group (8.4%). The majority of SAEs coded to the Psychiatric Disorders SOC. One subject in the paliperidone ER group had a SAE of homicide (committed homicide) in the post-double-blind treatment phase (9 days after last dose of study medication).

A lower percentage of subjects in the paliperidone ER group (5.1%) experienced TEAEs leading to discontinuation of treatment compared with subjects in the placebo group (8.4%). 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 group compared with the placebo group. TEAEs leading to dose adjustment that were reported by at least 2 subjects in the paliperidone ER group were akathisia, dystonia, and agitation.

The incidence of treatment-emergent EPS-related AEs was higher in the paliperidone ER group compared with the placebo group. Events that occurred more frequently in the paliperidone ER group than in the placebo group were akathisia and tremor. All of EPS-related AEs were considered to be mild or moderate in severity with the exception of dystonia (placebo: 1 subject) and tremor (paliperidone ER: 1 subject). No EPS-related event was reported as a SAE. One EPS-related AE (dystonia) led to discontinuation of 1 subject in the placebo group; no EPS-related events resulted in treatment discontinuation of paliperidone ER subjects. The changes from baseline to Week 6 and Week 6 LOCF in EPS rating scale scores (SARS, BARS, and AIMS) were similar in both 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. 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 slightly higher incidence in the paliperidone ER group (5.2%) compared with the placebo group (2.8%). No subject in either treatment group had a markedly abnormal elevation in ALT. One subject in the paliperidone ER group had a markedly abnormal elevation in alkaline phosphatase. However, there was a lower incidence of shifts from normal to high in alkaline phosphatase values in the paliperidone ER group compared with the placebo group. There were no other notable treatment group differences for other liver enzymes. Treatment-emergent AEs related to liver abnormalities were GGT increased and hepatic enzyme increased, reported by 1 (0.5%) subject each in the paliperidone ER group.

There was a lower incidence (≥5% difference) of shifts from normal at baseline to high at Week 6 LOCF in fasting glucose values in the paliperidone ER group compared with the placebo group. One subject each in the paliperidone ER and placebo group had a markedly abnormal elevation in fasting glucose during the study. Two subjects in the paliperidone ER group had glucose-related TEAEs (blood glucose increased, hyperglycaemia) during the study.

Assessment of ECG data did not reveal clinically significant QTc prolongation with paliperidone ER. No subject had a maximum postbaseline QTcLD or QTcF >480 msec. No subject experienced an increase of >60 msec from average predose QTcLD or QTcF values. One subject in the paliperidone ER group had a QTcB value that was >480 msec but ≤500 msec, and 1 subject in the paliperidone ER group experienced an increase of >60 msec from average predose QTcB. The incidence of subjects having a change from average predose meeting the classification of "concern" (30-60 msec) was similar between the treatment groups.

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 group compared with the placebo group, with treatment group differences most notable at Week 4 of the study. The incidence of weight gain ≥7% from baseline was greatest for both treatment groups at Week 6 (paliperidone ER: 7.5%, placebo: 3.8%). A slightly higher percentage of subjects in the paliperidone ER group (3.7%) experienced TEAEs of weight increased compared with subjects in the placebo group (2.1%).

At Week 6 LOCF, mean ISST total scores were similar to baseline for both groups, with a slight decrease in the paliperidone ER group (-0.4) and a very slight increase in the placebo group (0.1). At Week 6 and Week 6 LOCF the percentage of subjects who had ISST scores ≥1 was lower in the paliperidone ER group compared with the placebo group.

STUDY LIMITATIONS: This study investigated the efficacy and safety of paliperidone ER for the treatment of schizoaffective disorder over 6 weeks and does not provide information on longer term treatment.

CONCLUSION:

This study demonstrated the efficacy of paliperidone ER in subjects with an acute exacerbation of schizoaffective disorder. Superiority was consistently observed for paliperidone ER compared to placebo on change from baseline in PANSS total score, all PANSS factors (positive, negative, disorganized thought, hostility/excitement, and anxiety/depression), responder rates, and the overall CGI-S-SCA scale, as well as on the CGI-S-SCA positive, negative and depressive domains. Paliperidone ER was also effective in reducing manic and depressive symptoms in patients with prominent affective symptomatology, as assessed by changes from baseline to end point in YMRS total score and HAM-D-21 total score. Paliperidone ER was effective over a dose range of 3-12 mg, with significant therapeutic effects observed beginning as early as Day 4 of treatment.

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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