SYNOPSIS

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Name of Sponsor/Company	**Ortho-McNeil Janssen Scientific Affairs, LLC**
Name of Finished Product	**Paliperidone Extended Release [ER]**
Name of Active Ingredient(s)	**Paliperidone**

Protocol No.: CR041341, Phase IIIb

Title of Study: A Single-Arm Evaluation of the Safety of Paliperidone Extended-Release (ER) in Subjects with Schizophrenia or Schizoaffective Disorder with Hepatic Disease

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Publication (Reference): Not applicable

Study Period: 03 October 2007 to 26 February 2009; Database lock occurred on 24 April 2009.

Phase of Development: IIIb

Objectives: the primary objective of this study was to evaluate the tolerability and safety of flexibly-dosed paliperidone ER (pali ER) in subjects with schizophrenia or schizoaffective disorder with evidence of hepatic disease.

The secondary objectives of this study were to evaluate efficacy, patient reported outcomes (PRO) and other outcome parameters in subjects treated with pali ER.

Methods: the study was comprised of up to a 7-day Screening period followed by open-label treatment for 9 weeks, divided into two phases. Phase 1, lasting 4 weeks (Days 0-27), was a continuation of usual antipsychotic treatment (UAT [conventional or atypical oral antipsychotics other than pali ER, excluding clozapine and depot or long-acting injectable formulations]). Phase 2, which lasted 5 weeks, included both a 1-week cross-titration period and a 4-week period of pali ER alone.

During Phase 1, the present stability of liver function was assessed by laboratory evaluations of liver function tests (LFTs) taken during the Screening period and Visit 3 (Day 13) and Visit 4 (Day 24). Efficacy and other outcome parameters were also assessed.

Phase 2 consisted of a 1-week cross-titration from UAT to flexibly-dosed pali ER, followed by 4 weeks of pali ER alone. Pali ER was dispensed at Day 27 and assessments of safety and efficacy were performed. On Day 28, pali ER was initiated at a dose of 6 mg/day and the subjects' prior antipsychotic medication(s) dose(s) was tapered to discontinuation over no more than a 7-day period (by Visit 6 [Day 34]). The approach to the taper and discontinuation of prior antipsychotic(s) was at the investigator's discretion. Over the course of Phase 2, pali ER was flexibly-dosed. Changes in the pali ER dose were based upon clinician judgment beginning after the fourth pali ER dose (Day 31). Thereafter, the dose could be increased as

needed by 3-mg increments, at intervals no more frequently than every 5 days (i.e., after four doses), to a maximum of 12 mg/day. After Day 31, the pali ER dose could be reduced at any time to a minimum of 3 mg/day.

Number of Subjects (planned and analyzed): Planned: a sufficient number of subjects to ensure approximately 100 subjects would enter Phase 2. A total of 114 subjects entered Phase 1 and 84 subjects entered Phase 2.

Diagnosis and Main Criteria for Inclusion: subjects were male or female, at least 18 years old, with an established diagnosis of schizophrenia or schizoaffective disorder and stable active hepatic disease (Child-Pugh classifications of A [well compensated] or B [significant functional compromise]). Subjects must have been able to be managed as outpatients, and have aspects of disease management, which, in the investigator's opinion, could potentially benefit from a change in antipsychotic medication.

Test Product, Dose and Mode of Administration, Batch No.: 3 mg: lot 0627123; 6 mg: lot 0707704.

Reference Therapy, Dose and Mode of Administration, Batch No.: none

Duration of Treatment: pali ER was given for 5 weeks.

Criteria for Evaluation:

Efficacy, PRO and other outcome parameters: Positive and Negative Symptom Scale (PANSS), Clinical Global Impression of Severity and Change (CGI-S and CGI-C) scales, Personal and Social Performance (PSP) scale, Timeline Follow-Back (TLFB) for Alcohol, Medication Satisfaction Questionnaire (MSQ), 36-Item Short-Form Health Survey (SF-36), sleep Visual Analogue Scale (VAS), and Trail Making Test (TMT).

Safety variables: adverse events (AEs), pre-specified AEs, clinical laboratory tests including LFTs, vital sign measurements (blood pressure, radial pulse, temperature, weight), physical examination (including West Haven Criteria and ascites assessment), electrocardiogram (ECG), Barnes Akathisia Rating Scale (BAS), the Simpson Angus Rating Scale (SAS), and the Abnormal Involuntary Movement Scale (AIMS). The pre-specified AEs were the subset of all AEs that were considered potentially more relevant to antipsychotic treatment. Relevance was based on the application of rate thresholds to AEs listed in the manufacturers' Prescribing Information of all antipsychotic medications used in the trial for which there were AE listings in the product labeling. All labeled AEs occurring at a rate of ≥3% and ≥1.5 times the rate in placebo were included.

Statistical Methods: the sample size for this exploratory study was not based on statistical considerations but rather on precedent in the field for studies of special populations, in which samples of approximately 100 subjects are employed. Thus, sufficient subjects were to be recruited into the trial so that approximately 100 subjects would enter Phase 2 of the study, during which pali ER was given.

The primary objective of this study was to evaluate the tolerability and safety of flexibly-dosed pali ER in subjects with schizophrenia or schizoaffective disorder with evidence of hepatic disease. The comparison between Phase 1 and Phase 2 for safety and tolerability data was conducted on the primary safety analysis set (Safety Analysis Set), which included those subjects who received at least one dose of pali ER and had

any reported safety data (i.e., vital sign, labs, physical exam, movement disorder rating scales, or AE) reported in both Phase 1 and Phase 2. A secondary safety analysis set included all subjects who entered Phase 1 (i.e., Phase 1 Analysis Set).

The difference in the incidence of AEs between Phase 1 (UAT alone) and Phase 2 (pali ER with cross-titration) was assessed using time-to-event methodology (Kaplan-Meier estimates), AE incidence density, and cumulative mean function (CMF).

Kaplan-Meier estimates for the proportion of subjects who experienced AEs in Phase 1 (UAT alone) and separately in Phase 2 (pali ER with cross-titration) were obtained. The area under the curves for the Kaplan-Meier analysis (AUC_{KM}) of each phase was normalized by dividing the AUC_{KM} by the maximum duration of the phase then multiplied by 28.

The incidence density of AEs in Phase 1 (UAT alone) was defined as 28 multiplied by the number of subjects who experienced AEs in the Phase 1 (UAT alone) divided by the total number of days those subjects were at risk of experiencing AEs during Phase 1 of the study. The incidence density of AEs in Phase 2 (pali ER with cross-titration) was defined in a similar way.

The CMF represented the expected number of AEs per subject between time zero (start of a phase) and a follow-up time. CMF estimates for the average number of AEs per subject in Phase 1 (UAT alone) and separately in Phase 2 (pali ER with cross-titration) were obtained. In the case where multiple AEs occurred on the same day for a given subject, only one event was counted for the purpose of calculating CMF. The area under the CMF curve (AUC_{CMF}) of each phase was normalized by dividing the AUC_{CMF} by the maximum duration of the phase then multiplied by 28.

The 95% confidence interval (CI) for the difference in the analyses between Phase 1 and Phase 2 was estimated using bootstrap re-sampling methodology. A series of 1000 samples were created using sampling with replacement of subjects' complete records. The difference between Phase 1 and Phase 2 samples within each of the 1000 samples was calculated and ordered. The lower and upper limits of the 95% CI were defined as the 2.5^{th} percentile and 97.5^{th} percentile, respectively.

As there was a cross-titration period in Phase 2, any comparisons made between Phase 1 (UAT alone) and Phase 2 (pali ER with cross-titration) could be biased in favor of Phase 1 (UAT alone). Thus, the above analyses were also performed on UAT alone and pali ER alone.

The secondary objectives of this study were to evaluate efficacy, PRO and other outcome parameters in subjects treated with pali ER. This included PANSS, CGI-S, CGI-C, PSP, TLFB for Alcohol, MSQ, SF-36, sleep VAS, and TMT. These measures are summarized at all visits using mean, standard deviation (SD), median, minimum, maximum, change from UAT Baseline (Visit 2 [Day 0]), and change from pali ER Baseline (Visit 5 [Day 27]). The 95% CI based on the t-statistic, for the change from Baseline at each post-Baseline visit, is also presented.

RESULTS:

- A total of 207 subjects were screened, of which 114 subjects (55.1%) entered Phase 1 (UAT alone for 4 weeks). Eighty-five subjects (74.6%) completed Phase 1, and 84 subjects (73.7%) met the criteria to enroll into Phase 2 (cross-titration from UAT to pali ER for 1 week followed by pali ER alone for 4 weeks) from Phase 1.

- In the Safety Analysis Set (n=84) the majority of subjects were male: 57 (67.9%) and Black or African American: 50 (59.5%). The mean (SD) age was 48.9 (6.73) years, with a range of 26 to 61 years.

- In the Safety Analysis Set the Baseline mean (SD) PANSS and PSP total scores were 76.2 (13.36) and 56.7 (12.04), and a CGI-S grade of moderately ill was the most common and was reported by 36 subjects (42.9%).

- The most common primary etiology of chronic active liver disease was viral hepatitis, reported by 83 subjects (98.8%) in the Safety Analysis Set. In addition, the majority of subjects had stable liver disease based on Child-Pugh criteria, with 91 subjects (84.3%) in Class A (well-compensated) and 17 (15.7%) in Class B (significant functional compromise).

- In the Safety Analysis Set, subjects reported high rates of prior substance abuse, with past use reported in 69 (82.1%) for alcohol, 69 (82.1%) for marijuana, 47 (56.0%) for cocaine, 31 (36.9%) for stimulants, 30 (35.7%) for depressants, and 26 (31.0%) for heroin.

EFFICACY, PRO AND OTHER OUTCOME PARAMETERS:

- The changes in total PANSS score, psychopathology subscale and anxiety/depression scale scores were statistically significant from UAT Baseline (Visit 2 [Day 0]) to pali ER Baseline (Visit 5 [Day 27]). The changes from pali ER Baseline (Visit 5 [Day 27]) were statistically significant for PANSS total score and all subscale and factor scores at Visit 8 (Day 62) or early termination (ET).

- There was no change in CGI-S from UAT Baseline (Visit 2 [Day 0]) to pali ER Baseline (Visit 5 [Day 27]). The CGI-S scores improved significantly from pali ER Baseline (Visit 5 [Day 27]) to each follow-up time point.

- CGI-C score indicated no clinical change from UAT Baseline (Visit 2 [Day 0]) to pali ER Baseline (Visit 5 [Day 27]). CGI-C scores from pali ER Baseline (Visit 5 [Day 27]) showed minimal clinical improvement at Visit 7 (Day 48) and Visit 8 (Day 62) or ET.

- The PSP total score showed no mean change from UAT Baseline (Visit 2 [Day 0]) to pali ER Baseline (Visit 5 [Day 27]). Mean improvement in PSP total score from pali ER Baseline (Visit 5 [Day 27]) to Visit 8 (Day 62) or ET was statistically significant.

- No statistically significant difference was seen in TLFB from Screening to pali ER Baseline (Visit 5 [Day 27]) or from pali ER Baseline (Visit 5 [Day 27]) to each follow-up time point. Subjects had minimal alcohol consumption during the study.

- No statistically significant difference was seen in mean MSQ score from UAT Baseline (Visit 2 [Day 0]) to pali ER Baseline (Visit 5 [Day 27]). There was a statistically significant improvement in mean MSQ score from pali ER Baseline (Visit 5 [Day 27]) to Visit 8 (Day 62) or ET.

- There were no statistically significant changes for SF-36 from UAT Baseline (Visit 2 [Day 0]), except for the Social Functioning scale score. The Social Functioning scale score, showed a statistically significant improvement in mean score in the change from UAT Baseline (Visit 2 [Day 0]) to pali ER Baseline (Visit 5 [Day 27]). There were no statistically significant mean changes for SF-36 from pali ER Baseline (Visit 5 [Day 27]), except for the Physical Functioning and Social Functioning scale score. For the Physical Functioning scale score, a statistically significant decline in mean score was observed in the change from pali ER Baseline (Visit 5 [Day 27]) to Visit 8 (Day 62) or ET.

- For both the VAS – Drowsy or VAS – Sleep scores, there were no statistically significant mean changes from UAT Baseline (Visit 2 [Day 0]) to pali ER Baseline (Visit 5 [Day 27]) or pali ER Baseline (Visit 5 [Day 27]) to Visit 8 (Day 62) or ET.

- In both TMT Part A and B, there were no statistically significant mean changes from UAT Baseline (Visit 2 [Day 0]) to pali ER Baseline (Visit 5 [Day 27]) or pali ER Baseline (Visit 5 [Day 27]) to Visit 8 (Day 62) or ET.

SAFETY:

- The types of TEAEs reported were similar across all periods, although the frequencies of these events varied. Of the 84 subjects who formed the Safety Analysis Set, the number of subjects reporting at least one TEAE was: 27 subjects (32.1%) during UAT alone, 22 subjects (26.2%) during cross-titration, and 34 subjects (40.5%) during pali ER alone. The corresponding results for subjects reporting at least one pre-specified AE were: 23 subjects (27.4%) during UAT alone (4 weeks), 20 subjects (23.8%) during cross-titration (1 week), and 23 subjects (27.4%) during pali ER alone.

- The number of subjects who experienced an SAE was low and in the Safety Analysis Set was reported as none during UAT alone and during cross-titration, and two subjects (2.4%) (dystonia and psychotic disorder) during pali ER alone.

- Two subjects in the Safety Analysis Set experienced TEAEs that led to discontinuation from the study. These events were rash and dystonia which both occurred during pali ER alone.

- In the Safety Analysis Set the most commonly occurring treatment-related TEAE across all periods was tremor. This was reported by two subjects (2.4%) during UAT alone, three subjects (3.6%) during cross-titration, and four subjects (4.8%) during pali ER alone. With the exception of headache, no other treatment-related TEAEs were reported in three or more subjects across all periods.

- One severe TEAE was reported, an episode of dystonia during pali ER alone.

- Of the 114 subjects who formed the Phase 1 Analysis Set (i.e., all subjects who entered Phase 1), 33 subjects (28.9%) experienced at least one TEAE, and 24 subjects (21.1%) experienced at least one pre-specified AE potentially more relevant to antipsychotic treatment. The two most commonly occurring TEAEs (≥2% of subjects by preferred term) were weight increased (five subjects [4.4%]) and headache (three subjects [2.6%]). Two subjects (1.8%) experienced an SAE, one gastrointestinal hemorrhage and one cerebrovascular accident during UAT alone. Four subjects (3.5%) in the Phase 1 Analysis Set had TEAEs that led to discontinuation from the study. These events were blood creatinine increased, gastrointestinal hemorrhage, blood potassium decreased, and cerebrovascular accident.

- For the time to any AE analysis, the difference (95% CI) in the AUC_{KM} between Phase 1 (UAT alone) and Phase 2 (pali ER with cross-titration) was statistically significant: -5.78 (-8.43, -2.49), indicating a shorter average time to first AE during Phase 2 (pali ER with cross-titration) than Phase 1 (UAT alone). The difference (95% CI) in AUC_{KM} between Phase 1 (UAT alone) and pali ER alone was also statistically significant: -2.82 (-5.44, -0.06). For the time to any pre-specified AE analysis, the difference (95% CI) in AUC_{KM} between Phase 1 (UAT alone) and Phase 2 (pali ER with cross-titration) was statistically significant: -4.58 (-7.28, -1.54). However, the difference (95% CI) in AUC_{KM} between Phase 1 (UAT alone) and pali ER alone was not statistically significant: -0.66 (-2.88, 1.61).

- The incidence density for all AEs was 0.36 per person-month during Phase 1 (UAT alone), 0.61 per person-month during Phase 2 (pali ER with cross-titration), and 0.54 during pali ER alone. The difference (95% CI) between Phase 1 (UAT alone) and Phase 2 (pali ER with cross-titration) was statistically significant: 0.25 (0.03, 0.47). However, the difference (95% CI) between Phase 1 (UAT alone) and pali ER alone was not statistically significant: 0.18 (-0.04, 0.41). The incidence density for the pre-specified AEs was 0.29 per person-month during Phase 1 (UAT alone), 0.45 per person-month during Phase 2 (pali ER with cross-titration), and 0.33 per person-month during the pali ER alone periods. The difference (95% CI) between Phase 1 (UAT alone) and Phase 2 (pali ER with cross-titration) was not statistically significant: 0.16 (-0.02, 0.35). The difference (95% CI) between Phase 1 (UAT alone) and pali ER alone was also not statistically significant: 0.03 (-0.13, 0.19).

- The CMF of any AE and any pre-specified AEs was derived for Phase 1 (UAT alone), Phase 2 (pali ER with cross-titration), and pali ER alone. For all AE analysis, the difference (95% CI) in the AUC_{CMF} between Phase 1 (UAT alone) and Phase 2 (pali ER with cross-titration) was statistically significant: 12.73 (6.82, 17.48). The difference (95% CI) in AUC_{CMF} between Phase 1 (UAT alone) and pali ER alone was also statistically significant: 5.38 (1.28, 9.18). For the pre-specified AE analysis, the difference (95% CI) in AUC_{CMF} between Phase 1 (UAT alone) and Phase 2 (pali ER with cross-titration) was statistically significant: 8.54 (4.15, 12.27). However, the difference (95% CI) in AUC_{CMF} between Phase 1 (UAT alone) and pali ER alone was not statistically significant: 2.13 (-0.70, 5.01).

- In the BAS total score, there were no significant changes from UAT Baseline (Visit 2 [Day 0]) to pali ER Baseline (Visit 5 [Day 27]) and pali ER Baseline (Visit 5 [Day 27]) to Visit 8 (Day 62) or ET.

- In the SAS total score, the change from UAT Baseline (Visit 2 [Day 0]) to pali ER Baseline (Visit 5 [Day 27]) showed a statistically significant decrease. No SAS score changes from pali ER Baseline (Visit 5 [Day 27]) to Visit 8 (Day 62) or ET were statistically significant.

- In the AIMS total score, there were no statistically significant changes from UAT Baseline (Visit 2 [Day 0]) to pali ER Baseline (Visit 5 [Day 27]). In the AIMS total score, no significant change from pali ER Baseline (Visit 5 [Day 27]) was noted.

- Laboratory indices, including assessments of LFTs, were consistent with those observed in previous trials of pali ER in subjects without hepatic disease. In the Safety Analysis Set, no subject had a shift in transaminase values to > 3 times the ULN from Visit 1 (Screening) to Visit 4 (Day 24). One subject had a shift in AST from 2 to 3 times the ULN to > 3 to 4 times the ULN from Visit 4 (Day 24) to Visit 8 (Day 62) or ET. In the Phase 1 Analysis Set, three subjects had transaminase values shift to >3 to 4 times the ULN at Visit 4 (Day 24) and were therefore ineligible to continue to Phase 2.

- All other safety findings (vital signs, physical examinations and ECG evaluations) did not reveal any new safety signal in subjects with hepatic disease.

STUDY LIMITATIONS:

This exploratory, hypothesis-generating study is limited by its open-label single sequence, crossover design. Specifically, a stable regimen of UAT was compared to newly initiated treatment with pali ER. Further, pali ER was evaluated during and immediately after cross-titration and discontinuations from stable treatment with UAT, possibly, leading to carry-over and withdrawal effects. Finally, the protocol prohibited the patients from receiving pali ER, if they had evidence of hepatic disease progression during UAT. Thus exploratory safety comparisons and efficacy findings must be interpreted with caution.

CONCLUSION:

In conclusion, results from this exploratory, open-label, crossover study suggest that pali ER is well-tolerated in subjects with schizophrenia or schizoaffective disorder and stable active hepatic illness. Further, no new safety signals were detected in this hepatically compromised patient population. Additionally, improvements in psychiatric symptoms and functioning were observed after 4 weeks of treatment with pali ER. A future controlled study with placebo or active comparator could be conducted to further test the hypothesis that pali ER, with its limited hepatic metabolism, has a favorable risk-benefit profile for individuals with schizophrenia or schizoaffective disorder and hepatic illness.

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