SYNOPSIS

Name of Sponsor/Company	Xi'an-Janssen Pharmaceutical Ltd.
Name of Investigational Product	R092670 (paliperidone palmitate)

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Prepared by: Xi'an-Janssen Pharmaceutical Ltd.

Protocol No.: R092670SCH4018

Title of Study: Safety and Efficacy of Paliperidone Palmitate in 25-week Treatment on Chinese Patients with Schizophrenia: an Open-label, Single-arm, Multicenter Prospective Study

NCT No.: NCT01947803

Clinical Registry No.: CR100855

Coordinating Investigator(s): [redacted] MD, [redacted], P. R. China, [redacted]

Study Center(s): 13 sites in China

Publication (Reference): None

Study Period: 31 October 2013 to 16 March 2015. The database was locked on 30 April, 2015.

Phase of Development: Phase 4

Objectives:

Primary Objective

To evaluate the safety and tolerability of paliperidone palmitate in 25-week treatment of Chinese subjects with schizophrenia.

Secondary Objectives

1. To evaluate efficacy of paliperidone palmitate in 25-week treatment of subjects with schizophrenia using Positive and Negative Syndrome Scale (PANSS);

2. To assess efficacy of paliperidone palmitate in 25-week treatment of subjects with schizophrenia using Personal and Social Performance Scale (PSP).

Exploratory Objectives

1. To determine efficacy of paliperidone palmitate in 25-week treatment of subjects with schizophrenia using Clinical Global Impressions-Severity (CGI-S);
2. To evaluate the improvement of adherence from baseline to Day 64 (Week 9) or endpoint using Medication Adherence Rating Scale (MARS);
3. To assess the satisfaction of subjects and caregivers evaluated by Medication Satisfaction Questionnaire (MSQ) and the impact on treatment with paliperidone palmitate;
4. To evaluate subjects' life quality by Schizophrenia Quality of Life Scale (SQLS) and the impact on treatment with paliperidone palmitate;

5. To assess the burden on caregivers using Involvement Evaluation Qestionnaire-31 (IEQ-31) and the impact on treatment with paliperidone palmitate;
6. To evaluate the preference to long-acting injectable (LAI)- paliperidone palmitate by Attitude of Patients Preference to LAI (APL) and the impact on treatment with paliperidone palmitate;
7. To explore the pharmacoeconomic condition of subjects treated with paliperidone palmitate.

Methodology:

This was a Phase 4, non-randomized, open-label, single-arm, and prospective study on Chinese subjects with schizophrenia. The study was divided into 3 phases: a screening phase (up to 1 week), a treatment phase (25 weeks) and a follow-up phase (30 days). In the treatment phase, paliperidone palmitate was injected with a dose of 150 mg eq. on Day 1 and 100 mg eq. on Day 8 in the deltoid muscle, followed by a monthly flexible dose of 75, 100 or 150 mg eq. for injection (administered in the deltoid or the gluteal muscle), based on the subjects' tolerability and/or efficacy. All other antipsychotics were discontinued prior to the first dose of study drug, and were prohibited across the study.

Number of Subjects (planned and analyzed): The planned total sample size was 353 Chinese subjects. The actual sample size in each analysis set is presented as below.

Data Sets Analyzed: All Subjects Analysis Set

	Paliperidone Palmitate
Screened	403
Enrolled [a]	353
Safety set [e]	353 (100%)
Full analysis set [b]	345 (97.7%)
Per-protocol set [c]	193 (54.7%)
Pharmacoeconomic analysis set [d]	301 (85.3%)

[a] Enrolled subjects consisted of all subjects who had signed informed consent and met inclusion and exclusion criteria.
[b] Full analysis set consisted of all subjects who had received at least 1 dose of study drug and had at least one efficacy evaluation (except baseline).
[c] Per-protocol set was defined by excluding subjects who had major protocol violations or not completed the treatment and evaluations from the full analysis set.
[d] Pharmacoeconomic analysis set consisted of all subjects who had at least 1 dose of study drug and at least one IEQ-31, SQLS, or disease expenditures evaluation (except baseline).
[e] Safety set consisted of all subjects who had received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion: Subjects were men and women 18-65 years of age, inclusive, who had previous diagnosis of schizophrenia according to the "Text Revision" of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV-TR); and a PANSS total score between 60 and 120 (inclusive), currently either treated with or without any antipsychotics.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone palmitate for injection with a dose of 150 mg eq. on Day 1 and 100 mg eq. on Day 8 in the deltoid muscle, followed by a monthly flexible dose of 75, 100 or 150 mg eq. for injection in either the deltoid or the gluteal muscle alternatively up to Week 25. The batch No. were CJB5P00, CIB0G00, EAB6100 for 75 mg eq., CHB0T00, CEB5B00, DFB3600, CJB0P00, EAB6200 for 100 mg eq. and CEB3900, CFB5B00, CJB1S00, DBB2C00, DHB3L01, EBB6400, ECB6X00 for 150 mg eq.

Duration of Treatment: Subjects received paliperidone palmitate injection for up to 25-week.

Criteria for Evaluation:

Efficacy evaluations/endpoints:

- Changes in PANSS total score from baseline at each visit in the study population and the subgroups (with psychiatry history ≤5 years and >5 years);
- Changes in CGI-S score from baseline at each visit in the study population and the subgroups (with psychiatry history ≤5 years and >5 years);
- Changes in PSP score from baseline at each visit in the study population and the subgroups (with psychiatry history ≤5 years and >5 years);
- Changes in MSQ score from baseline on Day 64 (Week 9) or Day 176 (Week 25) in the study population and the subgroups (with psychiatry history ≤5 years and >5 years);
- Distribution of APL at baseline in the study population and changes in APL from baseline on Day 64 (Week 9) or Day 176 (Week 25);
- Distribution of MARS at baseline in the study population and changes in MARS score from baseline on Day 64 (Week 9) or Day 176 (Week 25).

Pharmacoeconomic evaluations:

- Changes in SQLS and IEQ-31 from baseline on Day 64 (Week 9) or Day 176 (Week 25) in the study population and the subgroups (with psychiatry history ≤5 years and >5 years);
- Disease expenditures comparison (pre- vs. post-treatment).

Safety evaluations:

Safety and tolerability evaluations included adverse events (AEs), vital signs, physical examination, suicide risk evaluation using Columbia-Suicide Severity Rating Scale (C-SSRS), 12-lead electrocardiogram (ECG), Abnormal Involuntary Movements Scale/ Barnes Akathisia Rating Scale/ Simpson Angus Scale (AIMS/BARS/SAS) and laboratory tests in this study. Incidence of Treatment-Emergent Adverse Events (TEAEs) was the major safety parameter.

Statistical Methods:

Sample size determination: The data on safety and efficacy of paliperidone palmitate in 500 Chinese subjects with schizophrenia treated for 6 months were required by Chinese Food and Drug Administration (CFDA). Data on paliperidone palmitate treatment from approximately 100 Chinese subjects in Study R092670PSY3011 (1-month formulation) and approximately 100 Chinese subjects in Asia Pacific Study R092670SCH3009 were expected. Therefore, additional data from approximately 300 Chinese subjects were required. Considering a 15% dropout rate, 353 subjects need to be enrolled in this study.

Efficacy analysis: The set for efficacy analysis was full analysis set (FAS) and per-protocol analysis set (PPS). FAS included all subjects who had received at least 1 dose of study drug and had at least one efficacy evaluation (except baseline). PPS was defined by excluding subjects who had major protocol violations or not completed the treatment and evaluations from FAS. FAS was the primary analysis set. The efficacy analyses were performed with the last observation carried forward (LOCF) of imputation for early withdrawals and missing visit assessments. The values and changes from baseline of PANSS total scores, PANSS subscale scores, PSP, CGI-S, MSQ, APL and MARS at each visit were summarized using

descriptive statistics. Efficacy assessments were compared between post-treatment and baseline using paired t test or Wilcoxon signed rank test at the 2-sided significance level of 5%. The change in score from the baseline at each visit was to be analyzed using an analysis of covariance (ANCOVA) model with psychiatry history (≤ 5 years, > 5years) as a factor, and baseline score as the covariate.

Pharmacoeconomic analysis: The set for pharmacoeconomic analysis was pharmacoeconomic analysis set (PAS). Changes in SQLS, IEQ-31 and disease expenditures were evaluated. The pharmacoeconomic assessments were compared between post-treatment and baseline using paired t test or Wilcoxon signed rank test at the 2-sided significance level of 5%. The change from the baseline score at each visit was to be analyzed using ANCOVA model with psychiatry history (≤ 5 years, > 5years) as a factor, and baseline score as the covariate.

Safety analysis: The set for safety analysis was safety analysis set (SS). For safety, the incidence of TEAEs was summarized. Special attention was given to the incidence of extrapyramidal symptoms (EPS)-related TEAEs, prolactin-related TEAEs and glucose-related TEAEs. Changes in vital signs from baseline were described. A listing of subjects with any laboratory results outside the reference changes was also provided. All the changes in ECG readings with clinically significant abnormalities were listed. Subjects with abnormal physical examination were also listed. Changes in C-SSRS and AIMS/BARS/SAS from baseline were also evaluated.

RESULTS:

STUDY POPULATION:

Dispositions

Overall, 403 subjects were screened in the screening phase and 353 of them entered the treatment phase as per inclusion/exclusion criteria, among them 242 and 111 subjects had psychiatry history ≤5 years and >5 years, respectively. Of the enrolled subjects, a total of 234 (66.3%) subjects completed the treatment and the most frequently reported reason for early withdrawal during the treatment was withdrawal of consent (36 [10.2%] subjects) followed by AEs (30 [8.5%] subjects), lack of efficacy (15 [4.2%] subjects), lost to follow-up (10 [2.9%] subjects), death (8 [2.3%] subjects) and major protocol deviation (8 [2.3%] subjects). Of the 234 subjects, 230 subjects completed the follow-up phase and only 4 subjects withdrew during the follow-up phase, due to lost to follow-up in 3 subjects and AEs in 1 subject.

Baseline characteristics

The means (SD) of body weight, height, and BMI in the 353 subjects in SS were 64.75 (12.311) kg, 165.70 (7.353) cm, and 23.53 (3.888) kg/m^2, respectively and they were all similar between the subgroups with psychiatry history ≤5 years and >5 years, with slightly numerically higher means (SD) of body weight (kg) and BMI (kg/m^2) in the subgroup with psychiatry history >5 years than ≤5 years (body weight: 66.32 [12.286] vs 64.04 [12.281]; BMI: 24.40 [3.952] vs 23.13 [3.800]). The sex ratio (male:female) was close to 1:1 in both SS and each subgroup. The mean age (SD) was 31.1 (10.52) years (range=17 to 62 years) in SS. The mean (SD) age was lower in the subgroup with psychiatry history ≤5 years (28.3 [9.40] years, range=17 to 60 years), compared with in the subgroup with psychiatry history >5 years (37.2 [10.32] years, range=21 to 62 years).

Protocol deviations

Overall, 62 (17.6%) of 353 subjects in SS had 1 or more major protocol deviations: 49 (13.9%) subjects had “others” reasons (mainly exceeding visit windows), 7 (2.0%) subjects included as ineligible subjects, 7 (2.0%) subjects met the withdrawal criteria but weren’t withdrawn from the study promptly, 7 (2.0%) subjects received protocol-prohibited concomitant medications/therapies, and 3 (0.8%) subjects received the incorrect treatment or dose.

Extent of exposure

The mean (SD) dose by excluding the dose on Day 1 and Day 8 was 118.69 (24.597) mg eq. during the study. The mean (SD) of last dose after Day 8 was 117.5 (28.14) mg eq. Subjects in the subgroup with psychiatry history ≤5 years were numerically lower in mean (SD) of average and last dose compared to ones in the subgroup with psychiatry history >5 years (average dose: 117.33 [24.428] vs 121.81 [24.822] mg eq.; last dose: 116.2 [28.13] vs 120.6 [28.10] mg eq.). The mean (SD) duration of exposure was 139.1 (65.80) days (median=176.0 days). Subjects in the subgroup with psychiatry history ≤5 years had a higher mean (SD) value of duration exposure (days) than ones in the subgroup with psychiatry history >5 years (144.8 [62.90] days vs 126.7 [70.43] days).

EFFICACY RESULTS:

The primary efficacy analysis, i.e. changes of PANSS total scores from baseline on Day 8, Day 36, Day 92, and Day 176 for LOCF data, was conducted in FAS. On Day 8 (Visit 3), the mean (SD) change from baseline in PANSS total score was -5.8 (7.97), which reached statistically significant level ($p<0.0001$). On Day 36 (Visit 4) and Day 92 (Visit 6), the mean (SD) changes from baseline in PANSS total score were -13.6 (13.02) and -21.5 (16.26), respectively, which represented clinically meaningful improvement with statistically significance ($p<0.0001$; $p<0.0001$). On Day 176 (Visit 9), the mean (SD) change from baseline in PANSS total score was -27.2 (18.30), which represented clinically meaningful improvement with statistically significance ($p<0.0001$) as well.

The means (SD) of PANSS total scores between the subgroups with psychiatry history ≤ 5 years and >5 years were similar at baseline (85.2 [13.53] vs 84.4 [12.74], p=0.6041). On Day 176 (Visit 9), the magnitude of mean reduction (SD) was greater in the subgroup with psychiatry history ≤5 years than with psychiatry history >5 years (-29.0 [18.77] vs -23.4 [16.70], p=0.0085) based on ANCOVA model. In each subgroup (psychiatry history ≤5 years and >5 years), the mean (SD) changes of PANSS total scores from baseline were statistically significant and clinically meaningful improvement was achieved at the end of treatment.

In the secondary efficacy analyses, changes of CGI-S scores from baseline on Day 8 (Visit 3), Day 36 (Visit 4), Day 92 (Visit 6), and Day 176 (Visit 9) in FAS were evaluated. On Day 8 (Visit 3), the mean (SD) change from baseline in CGI-S score was -0.2 (0.55), which was statistically significant ($p<0.0001$). On Day 36 (Visit 4) and Day 92 (Visit 6), the mean (SD) changes from baseline in CGI-S score were -0.7 (0.88) and -1.2 (1.06) respectively with statistically significance ($p<0.0001$; $p<0.0001$). On Day 176 (Visit 9), the mean (SD) change from baseline in CGI-S score was -1.6 (1.22), which represented clinically meaningful improvement with statistically significance ($p<0.0001$).

Changes of PSP scores from baseline on Day 8 (Visit 3), Day 36 (Visit 4), Day 92 (Visit 6), and Day 176 (Visit 9) in FAS were also evaluated as one of the major secondary efficacy endpoints. On Day 8 (Visit 3), the mean (SD) change from baseline in PSP score was 3.3 (7.26), which was statistically significant ($p<0.0001$). The mean (SD) changes from baseline in PSP score were 7.4 (10.24) on Day 36 (Visit 4) and 11.0 (13.09) on Day 92 (Visit 6) with statistically significance ($p<0.0001$; $p<0.0001$). On Day 176 (Visit 9), the mean (SD) change from baseline in PSP score was increased to 14.9 (15.04), which represented clinically meaningful improvement with statistically significance ($p<0.0001$).

PHARMACOECONOMIC RESULTS:

Overall, the pharmacoeconomic assessment is based on the 301 (85.3%) subjects in PAS.

At baseline, the mean (SD) SQLS score was 34.4 (15.01) and similar mean (SD) SQLS scores were observed between the subgroups with psychiatry history ≤5 years and >5 year (33.6 [13.70] vs 36.4 [17.60], p=0.1371). On Day 64 (Week 9), the mean (SD) change from baseline in SQLS score was -4.4 [12.96] and on Day 176 (Week 25), the mean (SD) change from baseline in SQLS score was -5.4 [15.11], which both showed statistical significance ($p<0.0001$; $p<0.0001$). The changes of SQLS scores showed

that clinically meaningful improvement of schizophrenia quality of life was achieved at the end of the treatment phase. Similar clinically meaningful improvement was also observed in the subgroups with psychiatry history ≤5 years and >5 years and similar magnitude of improvements were achieved between the 2 subgroups. In addition, reductions in IEQ-31 total scores showed clinically meaningful relief in burden on caregivers. Similar magnitude of relief was also observed in the 2 subgroups at the end of the treatment phase.

The comparison of disease expenditure at baseline and post-treatment (Day 176) in terms of institutionalization duration (days) and institutionalization cost (yuan) was also conducted. At baseline, the mean (SD) institutionalization duration (days) was 26.8 (28.27). At post-treatment (Day 176), the mean (SD) institutionalization duration (days) were increased to 35.8 (31.02), a mean (SD) change from baseline as 23.9 (34.60) with statistical significance ($p<0.0001$). The mean (SD) institutionalization cost (yuan) was 8213.3 (9260.04) at baseline. Although it was significantly increased to 10227.4 (8285.75) at post-treatment (Day 176) (mean change [SD]: 7539.0 [8756.28], $p<0.0001$), the percentage of institutionalized subjects over 6 months decreased from 26.9% at baseline to 12.9% at post-treatment.

SAFETY RESULTS:

Summaries of AEs and other safety data are based on the 353 (100%) subjects in SS. Overall, 181 (51.3%) subjects had TEAE(s) and 145 (41.1%) subjects had possibly related TEAE(s). Overall, the most frequently reported TEAEs by system organ class (SOC) were nervous system disorders (102 [28.9%] subjects). Among them, 54 (15.3%) subjects had extrapyramidal disorder and 37 (10.5%) subjects had akathisia by preferred term (PT). The other TEAEs by SOC included investigations (56 [15.9%] subjects including blood prolactin increase [31 (8.8%)], body weight gain [14 (4.0%)], transaminases increase [6 (1.4%)] and blood triglycerides increase [4 (1.1%)]), psychiatric disorders (56 [15.9%] subjects), general disorders and administration site conditions (13 [3.7%] subjects), gastrointestinal disorders (13 [3.7%] subjects), infections and infestations (12 [3.4%] subjects), hepatobiliary disorders (8 [2.3%] subjects), cardiac disorders (8 [2.3%] subjects), and eye disorders (7 [2.0%] subjects). Among them, blood prolactin increase in 31 (8.8%) subjects, body weight gain in 14 (4.0%) subjects, insomnia in 19 (5.4%) subjects, schizophrenia in 13 (3.7%) subjects, and upper respiratory tract infection in 8 (2.3%) subjects were among the more frequently-reported TEAEs by PT.

During the study, 24 (6.8%) subjects experienced treatment-emergent serious AE(s) (treatment-emergent SAE(s)). The most frequently reported treatment-emergent SAEs were psychiatric disorders (18 [5.1%] subjects) by SOC, with schizophrenia (11 [3.1%] subjects) as the most common treatment-emergent SAE by PT, followed by completed suicide (4 [1.1%] subjects with all events reported as doubtfully related or not related to paliperidone palmitate) and suicide attempt (3 [0.8%] subjects with 1 event each reported as possibly related, doubtfully related, and not related to paliperidone palmitate). In other SAEs by PT, only death (4 [1.1%] subjects) and extrapyramidal disorder (2 [0.6%] subjects) were reported in more than 1 subject. TEAEs leading to dose adjustment and study drug discontinuation were reported in 39 (11.0%) and 31 (8.8%) subjects, respectively. Psychiatric disorders (17 [4.8%] subjects) by SOC were the most frequently reported TEAEs leading to study drug discontinuation, and schizophrenia (10 [2.8%]) was the most frequently reported TEAE leading to discontinuation by PT.

Fatal cases were reported in 8 (2.3%) subjects. Among them, 4 (1.1%) subjects were reported to have completed suicide, all reported as doubtfully related or not related to paliperidone palmitate, and 4 (1.1%) additional subjects died in the study, including 2 subjects reported to have unexplained death and 2 reported as death. Both death events were reported as possibly related to paliperidone palmitate. In the 2 unexplained death events, one was doubtfully related to paliperidone palmitate and the other's relationship with paliperidone palmitate was not provided due to insufficient information.

In TEAEs of clinical interest, extrapyramidal symptoms (EPS), prolactin, and blood glucose-related TEAEs were reported in 96 (27.2%), 41 (11.6%) and 2 (0.6%) subjects, respectively. Extrapyramidal disorder (54 [15.3%] subjects) and akathisia (37 [10.5%] subjects) by PT were the 2 most frequently

reported TEAEs in hyperkinesia and parkinsonism categories, respectively. Likewise, blood prolactin increase (31 [8.8%] subjects) by PT was the most frequently reported prolactin-related TEAEs. Only 2 (0.6%) subjects were reported to have blood glucose increase by PT.

In clinical laboratory evaluations, most (70%) of the 353 subjects in SS had normal or non-clinically significant abnormal values for every parameter in hematology and urinalysis both at baseline and on Day 176 (Week 25). In blood chemistry, more than 50% of subjects had normal values for every parameter both at baseline and on Day 176 (Week 25) except for serum prolactin level (ug/L), of which the mean (SD) was increased from 40.738 (40.2877) at baseline to 71.841 (55.7461) on Day 176 (Week 25), with a change of 30.280 (54.7910). Subjects with normal (56 [15.9%]) or non-clinically significant abnormal (156 [44.2%]) prolactin at baseline remained unchanged on Day 176. Twelve (3.4%) subjects who were in the normal range of prolactin and 14 (4.0%) subjects with non-clinically significant abnormal value in prolactin at baseline were shifted to clinically significant abnormalities on Day 176.

In vital signs, the mean (SD) body weight was 64.75 (12.311) kg at baseline in SS and was gradually increasing at each visit during the study and reached 67.49 (12.591) kg on Day 206 (Week 29) with an additional increase of 1.98 (5.053) kg in the follow-up phase. Most of the subjects were maintained in the normal range in body weight at each visit. On Day 206 (Week 29), 13 (5.6%) subjects and 66 (28.6%) subjects had abnormal decrease and abnormal increase of body weight, respectively. No clinically significant changes were observed in SS for body temperature or respiration rate. More than 98% subjects were in the normal range in pulse rate and systolic/diastolic blood pressure. Abnormal changes were mostly not clinically significant. Prolongation of QTc interval (≥500 msec) was not observed during the study. The Columbia-Suicide Severity Rating Scale was conducted in only 28 out of the 353 subjects in SS and none of them had suicidal ideation or behavior.

In AIMS/BARS/SAS evaluation, more than 90% subjects had normal movement throughout the study and less than 20 subjects had minimal or mild abnormal movement at each visit. More than 75% subjects had no akathisia and no severe akathisia was reported throughout the study. The median in SAS total score were 0.00 throughout the study. Therefore, no trend indicative of parkinsonism was identified.

CONCLUSION(S): The efficacy and safety of paliperidone palmitate in 25-week treatment on Chinese subjects with schizophrenia has been validated in this study. Subjects' quality of life was clinically improved and burden on caregivers were relieved at the end of the treatment phase. The results of this study do not represent new identified risk for paliperidone palmitate. The benefit-risk assessment of paliperidone palmitate remains positive and unchanged for the approved indications.

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