SYNOPSIS

Name of Sponsor/Company:	Xian Janssen Pharmaceutical Ltd*
Product Name:	Invega Sustenna®
Name of Active Ingredient:	Paliperidone Palmitate

*In the whole report, 'sponsor' is used to represent Xian Janssen Pharmaceutical Ltd

Please find sponsor in contact information page of the study protocol.

Status: 1.0

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Prepared by: Xian Janssen Pharmaceutical Ltd.

Protocol number: R092760SCH4019

Title of Study: evaluation of efficacy, safety and tolerability of flexible doses of paliperidone palmitate in subjects with acute symptoms of schizophrenia previously unsatisfactorily treated by oral antipsychotics: a 13-week, open-label, single-arm, multicenter, prospective, interventional study, followed by a 1-year natural follow-up

Coordinating Investigator: [redacted], MD

Study Centers: This study was conducted in 22 sites led by Peking University Sixth Hospital

Study Period: Study duration was from 30 October, 2012 to 24 December, 2014. The date of database lock was 16 March, 2015.

Phase of Development: IV

Objectives:

Primary Objective:

To evaluate the efficacy of flexible doses of paliperidone palmitate in treating subjects unsatisfied with oral antipsychotics and having acute symptoms of schizophrenia by the response rate from baseline to week 13, i.e. the percentage of subjects with ≥30% improvement in PANSS (Positive and Negative Syndrome Scale) total score.

Secondary Objectives:

1. To evaluate the efficacy of paliperidone palmitate in the total population and subgroups with schizophrenia by CGI-S (clinical global impressions-severity) score, PANSS total score, PANSS subscale scores and Marder factor scores from baseline to Week 13;
2. To evaluate the effect of switching from different oral antipsychotics to paliperidone palmitate on compliance of subjects by MARS;
3. To evaluate the preference of subjects on paliperidone palmitate by MPQ and the effect of paliperidone palmitate treatment on MPQ;
4. To evaluate the satisfaction of subjects and caregivers on the treatment by MSQ and the effect of paliperidone palmitate treatment on MSQ;

5. To evaluate the functionality of subjects by PSP and the effect of paliperidone palmitate treatment on PSP;
6. To evaluate the burden of caregivers by IEQ and the effect of paliperidone palmitate treatment on IEQ;
7. To evaluate the effect of paliperidone palmitate treatment after completing the treatment of acute phase by exploring the percentage of subjects who continued paliperidone palmitate treatment in a long-term, real natural world, and analyzing different outcomes and relevant factors of continuing paliperidone palmitate and other oral antipsychotics treatments;
8. To explore efficacy and outcome-relevant factors in and after the acute phase by multivariate analyses;
9. To evaluate the safety and tolerability of paliperidone palmitate in the acute phase and long-term treatment.

Efficacy

Acute Phase:

- The response rate at Week 13 from baseline in the total population;
- The response rate at Week 13 from baseline in the risperidone/paliperidone extended-release (ER) tablets, olanzapine and others subgroups;
- The response rate at Week 13 from baseline in the newly diagnosed and non-newly diagnosed subgroups, based on the schizophrenia diagnosis time ≤3 years and >3 years;
- The changes of PANSS total scores, PANSS subscale scores and Marder factor scores at Week 13 from baseline in the total population and the subgroups;
- The changes of CGI-S, MSQ, PSP, IEQ, MARS and MPQ scores at Week 13 from baseline in the total population and the subgroups.

Follow-up Phase:

- The percentage of subjects continuing paliperidone palmitate treatment after the acute phase, and the causes of discontinuing paliperidone palmitate treatment;
- The relapse rate of subjects whose PANSS total scores were <70 at Week 13 in one-year treatment after the acute phase;
- The differences of PANSS, GCI-S, PSP, MARS, MPQ scores, relapse rates, satisfaction and disease burden between subjects continuing paliperidone palmitate treatment and switching to other oral antipsychotics;
- The relevant factors of continuing paliperidone palmitate treatment and outcomes by multivariate analysis after 1 year of the follow-up phase.

Safety:

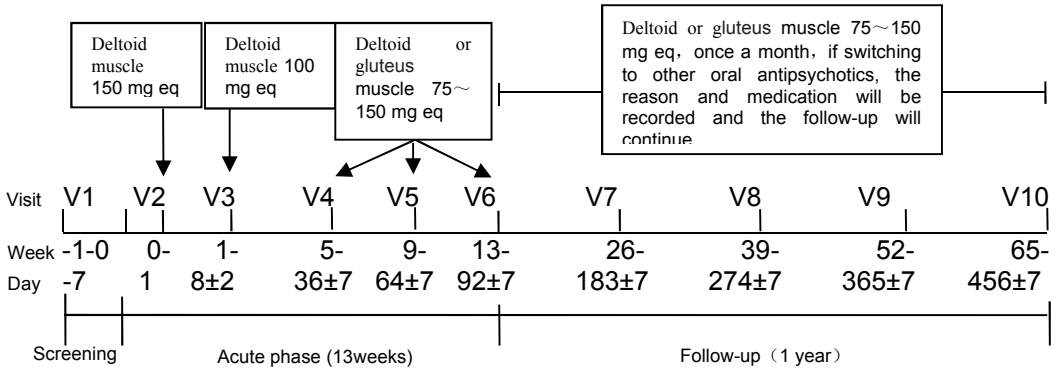
- Adverse events;
- Laboratory tests;

- Electrocardiogram (ECG);
- Vital signs;
- Physical examinations.

Hypothesis: The primary efficacy was defined as the response rate at Week 13 from baseline. The primary hypothesis was that 40% of subjects with acute symptoms of schizophrenia could meet the response criteria after paliperidone palmitate treatment for 13 weeks.

Methods: This was a multicentre, single-arm, open-label, prospective phase IV study. Competitive enrollments were conducted among the sites in this study and it was planned to enroll approximately 600 subjects. The study included three phases: a screening phase (up to 7 days), an acute phase (13 weeks) and a follow-up phase (1 year).

The subjects were those with acute symptoms of schizophrenia previously unsatisfied with oral antipsychotics treatment. During the screening phase and at baseline, the subjects were in acute attack stage with PANSS total scores from 70 to 120, inclusive. The eligible subjects were injected with paliperidone palmitate 150 mg eq. and 100 mg eq. in deltoid muscle on Day 1 and Day 8, respectively, followed by a monthly flexible dose of 75, 100 or 150 mg eq. injection according to the tolerability and/or efficacy. Previous oral antipsychotics were gradually reduced and to be withdrawn in two weeks after the first injection of paliperidone palmitate. After 13 weeks of the acute phase, the subjects entered the 1-year follow-up phase in natural environment. During this period, if subjects changed to other oral antipsychotics, the reasons were recorded and follow-ups were continued. PANSS, CGI-S, MSQ, PSP, MARS, MPQ, IEQ scores and relapse incidences were used to evaluate the efficacy. The primary efficacy endpoint was the response rate at Week 13 from baseline. Safety evaluations included adverse events, vital signs, physical examinations, laboratory tests and ECG.



Study Scheme

Number of Subjects:

The subjects included men and wowen with acute symptoms of schizophrenia previously unsatisfactorily treated by oral antipsychotics. Competitive enrollments were conducted among the multiple sites in this study and it was planned to enroll approximately 600 subjects. The actual number of subjects enrolled was 616. Full analysis set (FAS, N=610) was defined as the subjects who received at least 1 dose of the study drug and had at least 1 efficacy evaluation (except baseline). All

the subjects who entered the follow-up phase were included in the follow-up FAS (N=474), which was a population for efficacy and safety analyses. In addition, per-protocol set (PPS) in the acute phase (N=444) as the secondary population for efficacy analysis were generated, which included the subjects who completed Visit 6 (Week 13) without major protocol deviations in the acute phase.

Diagnosis and Main Criteria for Inclusion: The subjects had acute symptoms of schizophrenia previously unsatisfactorily treated with oral antipsychotics. The eligible subjects to participate in the study were in the acute attack stage during the screening phase and at baseline with PANSS total scores between 70 and 120, inclusive. The subjects with the following situations were excluded: main diagnosis of DSM-IV-TR Axis I diagnosis besides schizophrenia disorder, such as dissociative disorders, bipolar disorder, depression, schizoaffective disorder, schizophreniform disorder, autism, drug-induced type of mental illness, DSM-IV-TR diagnosis of active substance dependence (excluding nicotine and caffeine dependence) within 6 months before screening, or suicide attempts within 12 months before screening or clinically evaluated to have suicidal or violent behavior in the screening phase.

Study Product, Dose and Mode of Administration, Batch No.: The study product was Invega Sustenna® (paliperidone palmitate). The study product was white to grey injectable liquid, with specifications of 0.75 mL (0.75 mg eq.), 1.0 mL (100 mg eq.) and 1.5 mL (150 mg eq.). The paliperidone palmitate injectable liquid was white to grey suspension. Two types of needles- 1.5 inches No. 22 safety needle and 1 inch No. 23 safety needle were provided.

Control Treatment, Dose and Mode of Administration, Batch No.: Not applicable

Duration of Treatment: This study included three phases: the screening phase (up to 7 days), the acute phase (13 weeks) and the follow-up phase (1 year).

Efficacy Assessments: PANSS, CGI-S, MSQ, PSP, MARS, MPQ, IEQ scores and relapse incidences were used to evaluate efficacy. The primary efficacy endpoint was the response rate at Week 13 from baseline. At each visit, the clinical relevance of concomitant medications was reviewed. The subjects completed efficacy assessments at baseline, Day 8, Day 36, Day 64, Day 92, Day 183, Day 274, Day 365 and Day 456.

Safety Assessments: Safety evaluations included adverse events, vital signs, physical examinations, laboratory tests and ECG.

Statistical Methods: For subjects in the acute phase, the primary objective was to evaluate the improved efficacy based on PANSS total scores. The expected response rate was 40%. Taking the width (measurement accuracy) of two-sided 95% confidence interval as 20%, the sample size was approximately 93.

Assuming that in 5% of subjects the primary endpoint (based on PANSS total score) cannot be evaluated, the minimum sample size of subgroup was 98. To be able to explore the efficacy in the subgroups (risperidone/paliperidone ER tablets, olanzapine and others), and to assume the number of subjects in each subgroup was equal, at the same time, to explore certain additional diagnostic subgroups (newly diagnosed subjects versus not newly diagnosed based on the schizophrenia

diagnosis time ≤3 years or >3 years, respectively), therefore approximately 600 subjects would be enrolled in this study.

All efficacy assessments were based on the analysis sets during that phase. Efficacy assessments in the acute phase were based on the acute phase FAS (N=610), and support analysis were based on the acute phase PPS (N=444). Efficacy assessments in the follow-up phase were based on the follow-up FAS (N=474). LOCF method was used to fill missing data in efficacy assessments in the acute phase. LOCF method was not used to fill missing data in efficacy assessments in the follow-up phase. Unless otherwise specified, the hypothesis tests in this study were two-sided tests, taking 0.05 as the significance level. Analyzing the demographic, baseline characteristics and the scales, according to the drug use of subjects before entering the study (risperidone/paliperidone ER, olanzapine and others) and whether newly diagnosed subjects or not, subgroup analysis was made:

- Risperidone/paliperidone ER, olanzapine and others (others included subjects taking other antipsychotic drugs and subjects not taking any antipsychotic drugs in the last half year before entering the study).
- Newly diagnosed subjects and non-newly diagnosed subjects based on the schizophrenia diagnosis time ≤3 years and >3 years. The formula to calculate the schizophrenia diagnosis time was: (date of informed consent - date of diagnosis + 1)/365.25.

The primary efficacy endpoint was response rate at Week 13. Response rate was defined as the percent of responders. Responder was defined as subject who showed a reduction percentage change in PANSS total score ≥30%. The formula calculating reduction percentage change of PANSS total score after treatment: (PANSS total score at baseline - PANSS total score at Week 13)/(PANSS total score at baseline - 30) x 100%. Response rate at Week 13 was analyzed using descriptive statistics. 95% confidence interval of the rate was calculated by exact interval method of binomial distribution model. For the percent of subjects who had reduction percentage changes of PANSS total scores were ≥20% and ≥50% at Week 13, the same methods were applied. The analysis above was based on LOCF method, and the support analysis based on observed case data was aslo performed.

The frequencies and response rates at Week 1, Week 5 and Week 9, the frequency and response rate both at Week 1 and Week 5, the frequency and response rate after Week 5 in the acute phase, and the number and percentage of subjects who didn't have response during the acute phase were described. The same description was also performed on the ≥20% and ≥50% PANSS total score improvements, respectively. The analysis above was based on LOCF method, and support analysis based on observed case was also performed. The change of response rates over time (visit) was plotted to illustrate the cumulative improvement in the acute phase from baseline to each visit. Survival analysis was performed for time to first response, expressed as number of days from the first injection date to the first response, during the acute phase. Considering achieving response as an event and not achieving response or withdrawal from the study as a censored value, Kaplan-Meier plot was presented and the median time was summarized.

The change of each secondary efficacy endpoint in the acute phase from baseline to the end point was required to be analyzed on the observed case and LOCF data. For continuous variables, mean, standard deviation (SD), 95% confidence interval, number of cases, median, quartile 1, quartile 3, maximum and minimum at baseline, at each visit, the change from baseline to each visit and to the

end point of the study was described. Paired t-test was used to calculate p-values to analyze the change after the treatment. If the data did not meet the normal distribution, then paired rank test was used; for discrete variables, frequency and relative number (ratio, percentage and rate) at baseline and each visit was described. Paired Chi-square test was used for comparisons between baseline and post-treatment for 2-classification data, and multi-classification data for comparison of the change after the treatment was analyzed by Bowker test analysis.

For subjects who continued the paliperidone palmitate treatment, switched to other oral antipsychotics, and used the study drug again in the follow-up phase, frequencies and relative numbers (ratio, percentage and rate) were presented using descriptive statistics. For subjects who switched to other oral antipsychotics after entering the follow-up phase, survival analysis for time to first switch was performed. Kaplan-Meier plot was presented and the median time of switching to other oral antipsychotics were estimated.

For subjects who had PANSS total scores <70 at the end of the 13-week treatment and relapsed (relapse events or significant relapse events) in the follow-up phase, frequency and relative numbers (ratio, percentage and rate) were shown, and survival analysis for time to first relapse was also performed. The median time from entering follow-up to relapse was analyzed and plotted using Kaplan-Meier method.

During the follow-up phase, the use of primary and adjuvant antipsychotics was analyzed to explore different treatment options used in the population. The impact of exposure duration and injection times of paliperidone palmitate treatment on relapse was explored during the follow-up phase. Survival analysis for time to relapse was performed on subjects whose PANSS scores were <70 at Week 13. Considering relapse as an event, no relapse or withdrawal from the study as a censored value, the impact of the above-mentioned two factors (exposure duration or injection times) on relapse was analyzed using time-dependent Cox regression model.

Results

Study Population

A total of 652 subjects were screened and 616 subjects were enrolled in the study. Among them, 610 (99.0%) subjects were included in the acute phase FAS, and 444 (72.1%) subjects were included in the acute phase PPS, and 616 (100%) subjects were included in the acute phase SS. 474 (76.9%) subjects were included in the follow-up phase FAS.

In the acute phase of this study, the SS had 616 subjects and the FAS had 610 subjects. 477 subjects completed the acute phase (N=610, 78.2%) and 133 subjects withdrew from the acute phase (21.8%). The main reasons of early termination in the acute phase included lost to follow-up (47 subjects, 7.7%), informed consent withdrawal (27 subjects, 4.4%), lack of efficacy (19 subjects, 3.1%), adverse events (17 subjects, 2.8%), major protocol deviations (16 subjects, 2.6%), death (1 subjects, 0.2%) and others (2 subjects, 0.3%). 474 subjects entered the follow-up phase, 360 subjects completed follow-up (75.9%) and 114 subjects terminated early in the follow-up phase (24.1%). Early termination in the follow-up phase was mainly due to lost to follow-up (90 subjects, 19.0%), informed consent withdrawal (20 subjects, 4.2%), adverse events (1 subject, 0.2%), death (1 subject, 0.2%) and others (2 subjects, 0.4%).

In the FAS (N = 610) of the acute phase, the mean (SD) age was 31.5 (0.85) years (range: 17 to 64 years old), and the subjects was mainly aged from 18 to 25 years (226 subjects, 37.0%) and 31 to 50 years (227 subjects, 37.2%). The proportions of male and female subjects were comparable (male: 336 subjects, 55.1%; female: 274 subjects, 44.9%). Mean body mass index (SD) was 23.22 (3.773) kg/m^2 and the number of subjects with obesity (BMI ≥30 kg/m^2) was 41 (6.8%). The mean (SD) age of subjects at diagnosis of schizophrenia was 26.7 (9.41) years, and the mean (SD) psychiatric history was 5.3 (5.85) years. The majority (426 subjects, 70.4%) had DSM-IV-TR Axis I diagnosis of paranoid type, followed by the undifferentiated type (161 subjects, 26.6%), the tension-type (13 subjects, 2.1%) and the collapse type (5 subjects, 0.8%). The mean (SD) number of hospitalization in the 568 subjects over the past 12 months due to schizophrenia was 0.8 (0.96). According to previous antipsychotic treatment in the last 6 months before entering the study, 608 subjects who had received antipsychotic treatment were divided into three subgroups: subjects receiving risperidone/paliperidone ER treatment (263 subjects, 43.3%), subjects receiving olanzapine treatment (52 subjects, 8.6%), and subjects receiving other antipsychotics or did not receive antipsychotic medications within six months before the subjects were enrolled (293 subjects, 48.2%). The numbers of newly and non-newly diagnosed subjects in the FAS (N = 610) were 274 (44.9%) and 336 (55.1%), respectively. A total of 23 subjects had history of suicide (3.8%).

Extent of Exposure

In the FAS (N = 610) of the acute phase, the mean (SD) total injection dose was 536.4 (133.33) mg eq. excluding the first 2 injections (Day 1 and Day 8), the total number of subjects with injection(s) was 547 and the mean (SD) injection dose was 114.7 (23.41) mg eq. In the acute phase excluding the first 2 injections, the mean (SD) of model dose used most frequently was 114.7 (25.91) mg eq., and the mean (SD) of final dose was 114.8 (26.26) mg eq. The number of subjects who injected the study drug ≥5 times was 477 (78.2%), and the mean (SD) of medication duration (days) was 81.9 (30.66). 9 (1.5%) subjects had medication duration (days) ≤7, and 417 (68.4%) subjects had medication duration (days) ≥92.

In the FAS of the acute phase (N = 610), the dose of the first day was all 150 mg eq. At Week 1 (Day 8), the dose of 592 (99.8%) subjects was 100 mg eq. At Week 5 (Day 36), the doses were adjusted according to the subjects' personal situation, and the numbers (percentages) of subjects with the dose of 75, 100 and 150 mg eq. were 29 (5.4%), 334 (62.3%) and 173 (32.3%), respectively. At Week 9 (Day 64), the dose was adjusted according to the subjects' personal situation, and the numbers (percentages) of subjects with the dose of 75, 100 and 150 mg eq. were 44 (9.8%), 248 (55.1%) and 158 (35.1%), respectively. At Week 13 (Day 92), the dose was adjusted according to the subjects' personal situation, and the numbers (percentages) of subjects with the dose of 75, 100 and 150 mg of eq. were 44 (9.6%), 259 (56.4%) and 156 (34.0%), respectively.

In the FAS of the acute phase (N = 610), 75 (12.3%) and 62 (10.2%) subjects adjusted the doses at Week 9 (Day 64) and Week 13 (Day 92), respectively. Among them, 34 subjects increased the doses and 41 subjects decreased the doses at Week 9, and 31 subjects increased the doses and 32 subjects decreased the doses at Week 13.

In the FAS of the follow-up phase (N = 474), 143 subjects used the study drug, and the means (SD) of model and final dose were 107.5 (25.53) and 107.0 (25.42) mg eq., respectively. In the FAS of the

follow-up phase (N = 474), there were subjects who had dose adjustments in all months except for month 9, 11, and 12 in the 1-year follow-up phase, for example, 12 (2.5%) subjects in the first month, including 3 subjects with dose increase and 9 subjects with dose decrease. 7 subjects had dose adjustments in month 4, including 2 with dose increase and 5 with dose decrease. 3 subjects had dose adjustments in month 10, including 1 with dose increase and 2 with dose decrease.

Efficacy

Primary Endpoint

PANSS total score improvement from baseline to Week 13

In the FAS of the acute phase using LOCF data (N = 610), from baseline to Week 13 (N = 610), the number of responders was 443, and the response rate was 72.62% (95% CI: 68.899% to 76.127%). From baseline to Week 13 (N = 610), the number of subjects with ≥20% improvement in PANSS total score was 488, and the percentage was 80.00% (95% CI: 76.602% to 83.105%). From baseline to Week 13 (N = 610), the number of subjects with ≥50% improvement in PANSS total score was 322, and the percentage was 52.79% (95% CI: 48.738% to 56.809%).

The analysis based on observed case data from the FAS of the acute phase showed that, from baseline to Week 13 (N = 465), the number of responders was 391 subjects, and the response rate was 84.09% (95% CI: 80.822% to 87.629%). From baseline to Week 13 (N = 465), the percentages and 95% CIs of subjects with ≥20% and ≥50% improvements in PANSS total scores were 90.54% (95% CI: 87.936% to 93.38%) and 63.66% (95% CI: 59.371% to 68.312%), respectively.

In the PPS of the acute phase (N=444), at the end of treatment, the response rate (95% CI) and percentages (95% CIs) of subjects who had ≥20% and ≥50% improvements in PANSS total scores were 84.45% (95% CI: 80.683% to 87.745%), 90.72% (95% CI: 87.577% to 93.287%) and 63.57% (95% CI: 58.833% to 68.125%), respectively, which were similar with the results derived from the observed cases of the FAS.

Based on prior medications (risperidone/paliperidone ER, olanzapine and others) and whether the subjects were newly diagnosed or not, subgroups were made. In the FAS of the acute phase (N = 610), in the risperidone/paliperidone ER subgroup, at Week 13, i.e. at the end of treatment using LOCF data (N = 263), 191 subjects had responses, and the response rate was 72.62% (95% CI: 68.809% to 77.920%). In the olanzapine subgroup, at Week 13, i.e. at the end of treatment using LOCF data (N = 52), 36 subjects had responses, and the response rate was 69.23% (95% CI: 54.898% to 81.283%). In the others subgroup, at Week 13, i.e. at the end of treatment using LOCF data (N = 293), 214 subjects had responses, and the response rate was 73.04% (95% CI: 67.569% to 78.033%). The response rates of the 3 subgroups at the end of treatment were comparable.

In the newly-diagnosed subgroup using LOCF data (N=274), 205 subjects had responses at Week 13 and the response rate was 74.82% (95% CI: 69.243% to 79.846%). In the non-newly diagnosed subgroups using LOCF data (N=336), 238 subjects had responses at Week 13 and the response rate was 70.83% (95% CI: 65.655% to 75.640%). The response rate in the newly-diagnosed subgroup was slightly higher than that in the non-newly diagnosed subgroup at Week 13.

PANSS total score improvement at each visit in the acute phase

In the FAS of the acute phase (N = 610), at week 1, week 5, and week 9, the numbers of responders using LOCF data was 102, 314, 389, respectively, and the response rates were 17.1%, 51.5%, and 63.8%, respectively. The number of responders at both Week 1 and Week 5 was 94, and the response rate was 15.8%. After Week 5, the number of responders was 450, and the response rate was 73.8%. In the acute phase, the number of subjects who had no responses was 146, accounting for 23.9%. At week 1, week 5, and week 9, the numbers of subjects with ≥20% improvement in PANSS total score using LOCF data were 188, 403, and 462, respectively, and the percentages were 31.5%, 66.1%, and 75.7%, respectively. The number of subjects with ≥20% improvement in PANSS total score at both Week 1 and Week 5 was 171 and the percentage was 28.7%. After Week 5, the number of subjects with ≥20% improvement in PANSS total scores was 496 and the percentage was 81.3%. In the acute phase, the number (percentage) of subjects with <20% improvement in PANSS total score was 99 (16.2%). At Week 1, Week 5 and Week 9, the numbers of subjects with ≥50% improvement in PANSS total score using LOCF data were 25, 135, and 255, respectively, and the percentages were 4.4%, 25.1%, and 41.8%, respectively. The number of subjects with ≥50% improvement in PANSS total score at both week1 and week 5 was 25 and the percentage was 4.2%. After Week 5, the number of subjects with ≥50% improvement in PANSS total score was 330 and the percentage was 54.1%. In the acute phase, the number of subjects with <50% improvement in PANSS total score was 272 and the percentage was 44.6%.

The increase of the response rates over time (visit) at each visit in the acute phase was obvious at Week 1, Week 5 and Week 9, reaching highest at Week 5, and was relatively stable at Week 13.

Cumulative survival probability of the first response

The cumulative survival probability of the first response in the acute phase was analyzed. In the FAS of the acute phase (N = 610), at week 1 (day 8), week 5 (day 36), week 9 (day 64) and week 13 (day 92), the numbers of responders (the cumulative survival probability) were 82 (13.4%), 196 (33.0%), 359 (63.1%) and 443 (80.9%), respectively. Kaplan-Meier method was used to analyze the survival probability and the median time to show that on day 40 of the acute phase, the cumulative survival probability achieved 50%. The results based on the acute phase PPS were consistent with the acute phase FAS.

In conclusion, the response rates in the FAS of the acute phase had continuous improvement over time at all visits, and the subjects' mental symptoms were relieved.

Secondary Endpoints

All PANSS, CGI-S, MSQ, MARS, MPQ, PSP and IEQ scores showed that subjects had improvements in overall mental symptoms.

Acute phase

Change of PANSS total scores from baseline to week 13

In the FAS of the acute phase (N = 610) using LOCF data, the analysis showed at baseline the mean (SD) of PANSS total score was 91.8 (12.54), and the range was 70-120. At week 1 (day 8), week 5 (day 36), week 9 (day 64), and week 13 (day 92), the mean (SD) of PANSS total score was 82.2

(14.86), 71.4 (17.45), 65.5 (18.68), 60.9 (19.25), and the change of PANSS total score from baseline was -9.7 (10.60), -20.5 (15.45), -26.3 (17.81), -30.9 (19.51). The comparison between before and after treatment for each visit showed $p<0.001$ (based on paired rank test), which was statistically significant symptom improvement at 4 visits, i.e. week 1 (day 8), week 5 (day 36), week 9 (day 64), and week 13 (day 92). The improvement was significant with the prolongation of treatment.

Change of PANSS subscale scores from baseline to week 13

In the FAS of the acute phase (N = 610) using LOCF data, the analysis showed at baseline the mean (SD) of PANSS positive subscale score was 24.2 (5.50). At week 1 (day 8), week 5 (day 36), week 9 (day 64), and week 13 (day 92), the changes of PANSS positive subscale scores from baseline were -3.0 (3.65), -6.7 (5.42), -8.5 (6.03), and -9.9 (6.51), respectively. At baseline, the mean (SD) of PANSS negative subscale score was 23.1 (6.20). At week 1 (day 8), week 5 (day 36), week (day 64), and week 13 (day 92), the changes of PANSS negative subscale scores from baseline were -2.0 (3.36), -4.5 (4.72), -5.8 (5.50), and -7.0 (6.03), respectively. At baseline, the mean (SD) of general psychopathology subscale score was 44.6 (7.13). At week 1 (day 8), week 5 (day 36), week 9 (day 64), and week 13 (day 92), the changes of general psychopathology subscale scores from baseline were -4.6 (5.77), -9.3 (7.86), -12.0 (9.04), and -14.0 (9.95), respectively. The comparison for the three subscales between before and after treatment showed $p<0.001$ (based on paired rank test), which showed again the improvement was significant with the prolongation of treatment.

All analyses based on the observed case data from the FAS of the acute phase, PPS of the acute phase, and subgroups in the acute phase showed similar results.

Change of PANSS Marder factor scores from baseline to week 13

In the acute phase FAS using LOCF data, at baseline the mean (SD) of Marder factor-positive symptoms factor score was 28.9 (5.22). At week 1, the mean (SD) change of positive symptoms factor score was -3.0 (3.71), $p<0.001$. At week 5, the mean (SD) change of positive symptoms factor score was -6.9 (5.69), $p<0.001$. At week 9, the mean (SD) change of positive symptoms factor score was -9.0 (6.49), $p<0.001$. At week 13, the mean (SD) change of positive symptoms factor score was -10.7 (7.13), $p<0.001$.

For the acute phase FAS using LOCF data, at baseline the mean (SD) of Marder factor-negative symptoms factor score was 23.4 (6.36), and the range was 7-44. At week 1, the mean (SD) change of negative symptoms factor score was -2.1 (3.51), $p<0.001$. At week 5, the mean (SD) change of negative symptoms factor score was -4.5 (4.94), $p<0.001$. At week 9, the mean (SD) change of negative symptoms factor score was -6.0 (5.69), $p<0.001$. At week 13, the mean (SD) change of negative symptoms factor score was -7.1 (6.31), $p<0.001$.

In the acute phase FAS using LOCF data, at baseline the mean (SD) of Marder factor-cognition impairment factor score was 18.9 (4.37), and the range was 7-32. At week 1, the mean (SD) change of cognition impairment factor score was -1.7 (2.66), $p<0.001$. At week 5, the mean (SD) change of cognition impairment factor score was -3.7 (3.74), $p<0.001$. At week 9, the mean (SD) change of cognition impairment factor score was -4.8 (4.30), $p<0.001$. At week 13, the mean (SD) change of cognition impairment factor score was -5.7 (4.76), $p<0.001$.

In the acute phase FAS using LOCF data, at baseline the mean (SD) of Marder factor-uncontrolled excitement hostility factor score was 11.5 (4.05), and the range was 4-25. At week 1, the mean (SD) change of uncontrolled excitement hostility factor score was -1.9 (2.77), $p<0.001$. At week 5, the mean (SD) change of uncontrolled excitement hostility factor score was -3.5 (3.60), $p<0.001$. At week 9, the mean (SD) change of uncontrolled excitement hostility factor score was -4.2 (3.86), $p<0.001$. At week 13, the mean (SD) change of uncontrolled excitement hostility factor score was -4.7 (4.03), $p<0.001$.

In the acute phase FAS using LOCF data, at baseline the mean (SD) of Marder factor-anxiety/depression factor score was 9.0 (3.20), and the range was 4-20. At week 1, the mean (SD) change of anxiety/depression factor score was -1.0 (1.88), $p<0.001$. At week 5, the mean (SD) change of anxiety/depression factor score was -1.9 (2.43), $p<0.001$. At week 9, the mean (SD) change of anxiety/depression factor score was -2.4 (2.81), $p<0.001$. At week 13, the mean (SD) change of anxiety/depression factor score was -2.7 (3.06), $p<0.001$.

Overall, in the risperidone/paliperidone ER, olanzapine and others subgroups, the newly diagnosed and non-newly diagnosed subgroups, continuous improvement was observed at all visits in Marder factor scores. The acute phase PPS analysis also showed a similar result.

Change of CGI-S Score from baseline to each visit

In the acute phase FAS (N=610) using LOCF data, at baseline the mean (SD) of CGI-S score was 5.3 (0.73). At week 1, the mean (SD) change of CGI-S score was -0.5 (0.73), $p<0.001$. At week 5, the mean (SD) change of CGI-S score was -1.2 (1.05), $p<0.001$. At week 9, the mean (SD) change of CGI-S score was -1.5 (1.18), $p<0.001$. At week 13, the mean (SD) change of CGI-S score was -1.8 (1.30), $p<0.001$.

Overall, at each visit, CGI-S scores were observed to be improved significantly in different subgroups. Overall analysis of CGI-S score in the acute phase showed from week 1 to week 13, the number of subjects who had improvement of mental state (CGI-S scores decreased ≥ 1) increased from 255 (42.8%) to 509 (83.4%). The number of subjects who maintained basically unchanged decreased from 334 (56%) to 92 (15.1%). The number of subjects who had worse mental state (CGI-S scores increased ≥ 1) changed from 7 (1.2%) to 9 (1.5%).

Analyses of observed case data and in the acute phase PPS also showed similar results.

Change of MSQ Score from baseline to week 13 in the acute phase

At baseline, the mean (SD) of MSQ score in subjects was 3.9 (1.31). At week 13, the mean (SD) of MSQ score in subjects was 5.0 (1.1), $p<0.001$ and the change from baseline was 1.1 (1.57), $p<0.001$. At baseline, the mean (SD) of MSQ score in caregivers was 3.9 (1.20). At week 13, the mean (SD) of MSQ score in caregivers was 5.1 (1.06), $p<0.001$ and the change from baseline was 1.2 (1.51), $p<0.001$.

Overall, at week 13, medication satisfaction in both subjects, subgroups and caregivers were all improved significantly.

The change of MARS from baseline to week 13 in the acute phase

In the acute phase FAS, at baseline the number of compliant patient was 211 (34.7%). At week 13, the number of compliant patient increased to 328 (71.5%) and the proportion of compliant patient increased significantly ($p<0.001$). Overall, the patient compliance was improved significantly.

The analyses in the subgroups and PPS both showed the patient compliance was improved significantly.

Change of PSP total score and subscores in differnet dimensions in the acute phase from baseline to each visit

At baseline, the mean (SD) of PSP total score was 44.9 (13.65), which suggested different degrees of disease in subjects. At week 5 using LOCF data, the mean increase of PSP total score from baseline was 13.1 (14.15), $p<0.001$. At week 13 using LOCF data, the mean increase of PSP toal score from baseline was 19.3 (16.29), $p<0.001$.

The analyses of observed case data and in the acute phase PPS showed that subjects' functions were improved after the treatment and the improvements were better with prolongation of treatment.

Change of MPQ from baseline to week 13

In the acute phase FAS, from baseline to week 13, the percentage of subjects who preferred paliperidone palmitate tablets decreased from 39.1% (238/608) to 21.7% (100/461), and the percentage of subjects who preferred paliperidone palmitate injection changed from 60.9% (370/608) to 78.3% (361/461). The main reasons for subjects who preferred the tablets were "Tablets are not complicated for me", "I feel less pain taking tablets" and" I feel a sense of embarrassment to be reduced while taking tablets", and subjects who preferred injection thought "Injection is not complicated for me", "I do not need to think about medication", "My medications bring me fewer side effects" and "I do not worry about the sudden appearance of the symptoms of my illness". From baseline to week 13, the proportions of subjects who preferred deltoid injection and gluteal injection were similar. The percentage of subjects who preferred deltoid injection increased from 66.8% (405/608) to 70.0% (322/461) and who preferred gluteal injection decreased from 33.2% (201/608) to 30.0% (138/461). The main reasons for subjects who preferred deltoid injection were "Deltoid injection is not complicated for me", "I feel fewer embarrassment with deltoid injection" and "Deltoid injection is faster than gluteal injection", and subjects who preferred gluteal injection thought "Glueteal injection is not complicated for me", "I feel less pain in glueteal injection" and "Gluteal injection is faster than deltoid injection".

Follow-up phase

474 subjects entered the follow-up phase, including 123 (25.9%) subjects who continued to use the study drug during the follow-up phase (in the first month of follow-up phase, the study drug was still used), 331 (69.8%) subjects who took other oral antipsychotics, and 15 (3.2%) subjects who reused the study drug after receiving other oral antipsychotics. The median time during the follow-up phase to switching to other antipsychotics was 4.6 weeks. At the end of the acute phase, the number of subjects whose PANSS total scores were <70 (including all the subjects receiving oral administration and injection of paliperidone palmitate) was 367 (77.4%), and the number of subjects who had relapses during the follow-up phase was 46 (12.5%). Hazard Ratio (95% CI) for exposure duration

(months)'s effect before the first relapse on time to relapse was 0.9067 (0.8266, 0.9945). Hazard Ratio (95% CI) for injection times' effect before the first relapse on time to relapse was 0.8978 (0.8174，0.9862), which suggested that the paliperidone palmitate treatment can reduce the risk of relapse.

Follow-up phase assessments

PANSS total score, PANSS Marder factor scores, CGI-S score, PSP scores, MARS, MPQ, and MSQ score were all maintained as that at the end of acute phase, and even improved to some extent. Schizophrenia pathological symptoms, severity of illness, subjects' and caregivers' medication satisfaction, drug compliance, attitude and preference of drug, burden on caregivers were all significantly improved.

In summary, in treating subjects who were not satisfied with oral antipsychotic treatment and had acute symptoms of schizophrenia with paliperidone palmitate, psychopathology symptoms of schizophrenia subjects were significantly improved. The improvements in three subgroups of previous risperidone/paliperidone ER, olanzapine and others and two subgroups of newly diagnosed subjects and non-newly diagnosed subjects were basically the same.

Safety

The safety set of the acute phase included 616 subjects. TEAEs occurred in 198 (32.1%) subjects, of which 150 (24.4%) subjects had possibly treatment-related TEAEs. In this study, one (0.2%) subject died during the acute phase. 14 (2.3%) subjects had serious TEAEs and 17 (2.8%) subjects had TEAEs leading to treatment discontinuation or withdrawal from the study.

A total of 150 (24.4%) subjects had the treatment-related (including possibly related/probably related/very likely related) TEAEs during the acute phase, of which 99 (16.1%) sbujects were possibly related, 20 (3.2%) subjects were probably related, and 31 (5.0%) subjects were very likely related. The adverse events related to the study drug mainly occurred in the nervous system disorders (71 subjects, 11.4%), particularly extrapyramidal disorder (50 subjects, 8.1%), followed by psychiatric disorders (35 subjects, 5.6%), mainly insomnia (19 subjects, 3.1%) and anxiety (8 subjects, 1.3%). 17 (2.8%) subjects had TEAEs leading to treatment discontinuation or withdrawal from study during the acute phase, mainly psychiatric disorders (9 subjects, 15%), nervous system disorders (4 subjects, 0.6%), and cardiac disorders (2 subjects, 0.3%). The most commonly reported TEAE PTs were schizophrenia (6 subjects, 1.0%) and extrapyramidal disorder (3 subjects, 0.5%).

The follow-up phase SS included 474 subjects. TEAEs occurred in 69 (14.6%) subjects. Possibly related TEAEs occurred in 18 (3.8%) subjects. During follow-up, 1 subject (0.2%) died, 14 (3.0%) subjects had serious TEAEs, and 4 (0.8%) subjects had TEAEs leading to study drug discontinuation.

In this study, 2 subjects reported deaths, and they were doubtfully related to the study drug assessed by the investigator.

The overall incidence of adverse events of clinical interest in this study was low:

The acute phase:

(1) Prolactin-related adverse events: in the acute phase, a total of 9 subjects reported prolactin-related adverse events. 5 (0.8%) male subjects had blood prolactin increased, 4 female subjects had menstrual disorder (1 [0.2%] subject), menstrual delayed (2 [0.3%] subjects), irregular menstruation (1 [0.2%] subject), and oligomenorrhoea (1 [0.2%] subject).

(2) Extrapyramidal symptoms (EPS)-related adverse events: in the acute phase, 73 (11.9%) subjects developed EPS-related adverse events, including 55 (8.9%) subjects with Parkinsonism and 18 (2.9%) subjects developing hyperkinesia.

(3) Glucose-related adverse events: Only 1 patient had a blood glucose increase event in the acute phase, and according to the investigator's judgment, it was doubtfully related to the study drug.

The follow-up phase:

(1) Prolactin-related adverse events: there were 7 prolactin-related adverse events in the follow-up phase.
(2) EPS-related adverse events: 15 (3.2%) subjects had EPS-related adverse events, including 10 (2.1%) subjects with Parkinsonism.

There were no glucose-related adverse events reported in the follow-up phase.

Laboratory tests, vital signs, physical examinations and ECG were performed at screening, at week 13, in month 12 of the follow-up phase, and when early withdrawal from the study. The laboratory test results in all subjects during each visit were good. Abnormal physical examination occurred in musculoskeletal, eyes, skin, abdomen, head, neck, and thyroid system, etc.

At visits in the acute phase, musculoskeletal disorders included hypermyotonia in both upper limbs at week 13 and femur operation at week 9. The abnormal results of skin mainly included old operative scar at week 5 and week 13, rash and lipoma at week 13, etc. The abnormal results of abdomen included operative scar and fatty liver at week 13, etc. The abnormal results of head, neck, and thyroid system included old operative scar, etc. Most of the abnormal vital signs were abnormal body weight, abnormal pulse rate increase and abnormal systolic and diastolic blood pressure decrease. Subjects who had normal or abnormal values without clinical significance at baseline but had abnormal values with clinical significance at week 13 of the acute phase in laboratory tests included as follows:

Hematology: 1 subject each in white blood cell count, neutrophil count, percentage of neutrophils, hematocrit, and lymphocyte count;

Urinalysis: 2 subjects in urine white blood cell;

Blood Chemistry: 5 subjects in alanine aminotransferase, 4 subjects in aspartate aminotransferase, 1 subject each in γ-glutamyl transferase, lactate dehydrogenase, and blood uric acid, and 2 subjects in alkaline phosphatase

ECG of most subjects was normal or abnormal with no clinical significance, and abnormal ECG with clinical significance was found in only few subjects (4 subjects, 0.6%) at week 13, such as sinus bradycardia with arrhythmia. In the follow-up phase, abnormal ECG with clinical significance was found in 9 subjects.

Abnormal results in physical examinations in the follow-up phase: The abnormal results in physical examination with clinical significance mainly included operative scar and lipoma.

Abnormal results in vital signs in the follow-up phase:

The abnormal results in body weight included abnormal body weight loss in 16 (3%) subjects and abnormal body weight gain in 62 (13%) subjects in month 3; abnormal body weight loss in 13 (3%) subjects and body weight gain in 73 (15%) subjects in month 6; abnormal body weight loss in 11 (2%) subjects and abnormal body weight gain in 87 (18%) subjects in month 9; abnormal body weight loss in 12 subjects and abnormal body weight gain in 74 subjects in month 12. Abnormal pulse rate increase occurred in 2 (<1%) subjects each in month 3 and 12, and 1 (<1%) subject each in month 6 and 9. Abnormal systolic pressure decrease occurred in 2 (<1%) subjects in month 3 and 1 (<1%) subject in month 9.

Subjects who had normal or abnormal values without clinical significance at baseline, but had abnormal values with clinical significance in month 12 of the follow-up phase in laboratory tests included as follows:

Hematology: 2 subjects in white blood cell count, 1 subject each in neutrophil count, percentage of neutrophils, hematocratic, hematoglobin, lymphocyte count, percentage of lymphocytes and palette count.

Urinalysis: 1 subject each in urine protein and urine ketones, 3 subjects in urine red blood cell, and 4 subjects in urine white blood cell.

Blood chemistry: 5 subjects in alanine aminotransferase, 3 subjects in aspartate aminotransferase, 3 subjects in γ-gultamyl transferase and 2 subjects in blood uric acid.

There were no safety concerns according to latoratory test results at each visit.

The abnormal results with clinical significance in ECG in month 12 of the follow-up phase were found in 7 (1%) subjects.

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