SYNOPSIS

Name of Sponsor/Company	Janssen Asia Pacific Medical Affairs, a Division of Johnson and Johnson Pte Ltd*
Name of Finished Product	INVEGA SUSTENNA
Name of Active Ingredient(s)	JNJ-16977831-AAA; paliperidone palmitate

* The legal entity acting as the sponsor for studies of Janssen Asia Pacific Medical Affairs may vary. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

Status: Approved

Date: 11 December 2014

Prepared by: Janssen Asia Pacific Medical Affairs, a Division of Johnson and Johnson Pte Ltd

Protocol No.: R092670-SCH-4009

Title of Study: An Open-label, Prospective, Non-comparative Study to Evaluate the Efficacy and Safety of Paliperidone Palmitate in Subjects with Acute Schizophrenia

Study Name: PREVAIL study

NLM Identifier: NCT01527305

Clinical Registry Identifier: CR100739

Coordinating Investigator(s): Huafang Li, MD, PhD: Shanghai Mental Health Center, Shanghai, China

Study Center(s): The study was conducted at 27 study centers in 4 Asian countries (6 sites in China, 10 sites in Korea, 3 sites in Malaysia, and 8 sites in Taiwan).

Publication (Reference): None

Study Period: Study conduct was from 13 June 2012 to 31 December 2013. The database lock was on 12 March 2014.

Phase of Development: 4

Objectives: The primary objective was to evaluate the efficacy of paliperidone palmitate given once monthly, as measured by the change in Positive and Negative Syndrome Scale (PANSS) total score from baseline to end point, in schizophrenic inpatients who have experienced recent exacerbation (within past 4 weeks) of acute schizophrenia.

Secondary objectives were to evaluate the clinical responses by the following assessment variables after administration of paliperidone palmitate to acute schizophrenic subjects:

Efficacy

- The PANSS responder rate, as measured by the percentage of subjects with at least a 30% reduction from baseline in PANSS total score;
- Changes in PANSS factor scores and PANSS subscale scores;
- Change in global severity of illness using the clinical global impression-severity (CGI-S) score;
- Change in Personal and Social Performance (PSP) scale score and ratio of mild degree dysfunction ($71 \leq$ score ≤ 100), varying degree difficulty ($31 \leq$ score ≤ 70), and poor level function (score ≤ 30) based on PSP score;

- The time to readiness for hospitalization discharge for inpatients using the readiness for discharge questionnaire (RDQ) scale;
- The occurrence of drug discontinuation.

Safety

- To explore incidence of adverse events;
- To explore changes in vital signs, weight measurements, and physical examination.

Other

- To describe the usage of concomitant psychotropic medication.

Hypothesis: The null hypothesis was that there is no difference in the PANSS total score between baseline and end point visits after administration of paliperidone palmitate to acute schizophrenic subjects. Note: The primary efficacy endpoint defined in Section 11.6 of the protocol aligns with the null hypothesis. The mean of at least 6 points in the PANSS total score improvement between baseline and end point stated in Section 2 of the protocol was used for sample size justification.

Methodology: This was an open-label, prospective, observational study conducted at multiple sites in 4 Asian countries (China, South Korea, Malaysia, and Taiwan) that evaluated paliperidone palmitate in subjects with schizophrenia in an acute phase of exacerbated illness. The planned total sample size was approximately 232 subjects as a single group. The clinical study design comprised a screening period of up to 7 days, a 13-week treatment period and a study completion or early withdrawal visit.

Subjects who are hospitalized for an acute exacerbation of schizophrenia within 4 weeks prior to screening will be enrolled. Each subject must have a PANSS total score of ≥60 or CGI-S score of ≥4 (moderately ill) at screening. Hospitalized subjects were switched from their current antipsychotic therapy to paliperidone palmitate long-acting injection on Day 1. Oral antipsychotic supplementation was not required during the initiation of paliperidone palmitate injection and any previous oral antipsychotic therapy was discontinued prior to Day 1; however, if needed, risperidone or paliperidone extended-release (ER) (oral tablet) were to be used to support the tapering process beginning from the screening evaluation up to Day 1.

Enrolled subjects received paliperidone palmitate long-acting injection (LAI) on 4 study days:

Study Day	Fixed/Flexible	Dose	Sites (alternating sides)
Day 1	Fixed	150 mg eq.	Deltoid muscle
Day 8	Fixed	100 mg eq.	Deltoid muscle
Day 36	Flexible	50, 75, 100, or 150 mg eq.	Deltoid or gluteal muscle
Day 64	Flexible	50, 75, 100, or 150 mg eq.	Deltoid or gluteal muscle

Number of Subjects (planned and analyzed): The planned sample size was 232 subjects. The number of subjects enrolled was 218 and 6 subjects were subsequently screen failures. The intent-to treat (ITT) analysis set (N=212 subjects) was defined as all study subjects who receive at least 1 dose of the study drug, regardless of compliance with the protocol and was used for both efficacy and safety analysis. The Per Protocol analysis set (N=179 subjects) was generated for additional analyses since more than 5% of subjects (33 [15.6%]) had a major protocol deviations (MPD), which were defined as subjects who: did not satisfying the eligibility criteria, developed withdrawal criteria during the study but were not withdrawn, received the wrong treatment or incorrect dose, or received an excluded concomitant treatment.

Diagnosis and Main Criteria for Inclusion: Subjects were inpatients hospitalized with an acute exacerbation of schizophrenia within 4 weeks of screening. Patients had a PANSS total score of ≥60 or CGI-S score of ≥4 (moderately ill) at screening in order to be eligible for participation. Patients who had a primary active Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) Axis I

diagnosis other than schizophrenia or had received depot antipsychotics (including paliperidone palmitate) within 1 month of the screening visit were excluded.

Test Product, Dose and Mode of Administration, Batch No.: The test product was INVEGA® SUSTENNA® (paliperidone palmitate). The test product was a once-monthly extended-release injection and was supplied by the Sponsor in prefilled syringes of 50 mg (0.5 mL), 75 mg (0.75 mL), 100 mg (1.0 mL), and 150 mg (1.5 mL). Paliperidone palmitate is white to almost white powder. The aqueous suspension is white to off-white. Safety needles were provided separately as a 1½-inch 22 gauge needle and a 1-inch 23 gauge safety needle. The batch numbers for drug supplies by country are:

Country	Batch numbers
China	BLB0Y00, CBB0P00, BKB4R00, CDB7400, CEB5B00, BKB4S00, CBB4H00, CFB5B00
Korea	CIB2200, CDB4000, BABK000, CEB2L00, BKB4Q00, BABK001, CEB5B00, BKB4R00, BABK001, CEB3900, BABK002
Malaysia	BEBK000, CAB3N00, CEB5A00, CAB3P00, CHB0T01, CEB3900, CAB1K00
Taiwan	CBB0N01, BJB3Z00, CAB3N00, CAB3P00, CAB1H00

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.

Duration of Treatment: The clinical study design comprised a screening period of up to 7 days, a 13-week treatment period and a study completion or early withdrawal visit.

Efficacy Evaluation: Treatment effectiveness was evaluated by analyzing data from the PANSS, CGI-S, PSP, and RDQ. Concomitant medications were reviewed for clinical relevance at each study visit. Subjects completed efficacy assessments at Screening, on Day 1, Day 4, Day 8, Day 36, Day 64 and Day 92.

Positive and Negative Syndrome Scale (PANSS). The 30-item PANSS assesses symptoms of schizophrenia and was administered by the investigator or other qualified rater. The PANSS consist of 3 subscales: positive (7 items; 49 points), the negative (7 items; 49 points), and the general psychopathology subscale (16 items; 112 points). Each item is rated on a scale of 1 (absent) to 7 (extreme). The total score (sum of all the 30 items) ranged from 30 to 210. Five subscales of the PANSS, derived by factor-analysis were obtained and include 5 factors: negative symptom, positive symptom, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression factor scales.

Clinical Global Impressions-Severity (CGI-S) Scale. The CGI-S scale was administered by a clinician or qualified rater to assess disease severity. The question “Considering your total clinical experience with this particular population, how mentally ill is this patient at this time”, has 7 possible responses ranging from not ill (1) to severely ill (7).

Personal and Social Performance (PSP) Scale. The clinician rated and administered PSP instrument provides an overall rating of personal and social functioning on a continuum from grossly impaired functioning to excellent functioning using 4 domains: 1) socially useful activities, including work and study, 2) personal and social relationships, 3) self-care, and 4) disturbing and aggressive behavior. The degree of dysfunction a subject exhibits during the month prior to the visit is rated on a 6-point scale (1=absent, 2=mild, 3=manifest, 4=marked, 5=severe, 6=very severe). The final total score ranges from 1 – 100 (71 – 100 indicating mild, good or excellent degree of dysfunction, 31 – 70 indicating varying degrees of difficulty, and ≤30 indicating ‘such a poor level functioning that intensive supervision is required’).

Readiness for Discharge Questionnaire (RDQ) Scale. The clinician administered RDQ was a brief psychometric clinical research tool for assessing readiness for hospital discharge for inpatients with schizophrenia. The 6-item RDQ consists of 5 items assessing suicidality/homicidality, control of aggression/impulsivity, activities of daily living, independence in medication-taking, delusions/hallucinations interfering with functioning on a 4-point scale (1=strongly agree, 2=agree,

3=disagree, 4=strongly disagree), and 1 item assessing CGI-severity ≤4 status using a binary "yes/no" response. Using all 6 items as a guide, the clinician provides a final overall "yes/no" answer to the question 'is the subject ready for discharge'.

Safety Evaluation: Safety included evaluation of adverse events, physical examination, vital signs, weight (BMI), pregnancy testing, and concomitant medications.

Statistical Methods: A sample size of 185 subjects achieves 90% power to detect a mean difference of 6 units between baseline and end point PANSS total scores with an estimated standard deviation of 25 units with a significance level of 0.05 using a two-sided one-sample t-test. Assuming approximately 20% of subjects were missing either baseline or all post-baseline PANSS assessments, approximately 232 subjects were needed to be enrolled.

All efficacy and safety analyses were based on the intent-to-treat (ITT) analysis set (N=212). The Per-Protocol (PP) analysis set (N=177) consisted of all ITT subjects without major protocol deviations (MPDs) and was used to verify the efficacy findings regardless of patients who took excluded concomitant medications. The analysis was divided into 2 subgroups according to duration of schizophrenic illness: recently diagnosed (≤3 years) and chronically ill (>3 years) subjects.

The primary efficacy null hypothesis was that there is no difference in the PANSS total score between baseline and end point visits after administration of paliperidone palmitate to acute schizophrenic subjects.

The primary efficacy end point is the change in PANSS total score from baseline at end point (Week 13). The last post-baseline observation in the treatment period was used as the LOCF (last observation carried forward) end point (Week 13 LOCF) for the primary analysis of change in PANSS total score. The change from baseline to Week 13 LOCF end point in PANSS total score was summarized. The within group differences were analyzed using a paired t-test and accompanying 95% confidence interval (CI) for the mean differences.

For the secondary efficacy analyses, the PANSS responder rate (percentage of subjects with at least a 30% reduction from baseline in the PANSS total score at end point) was summarized. In addition to 30% response rate, 20%, 40%, and 50% response rates based on PANSS total score were summarized. For PANSS factor scores, CGI-S, and PSP, the actual values and changes from baseline were summarized descriptively for both observed and LOCF data. The differences for change from baseline were evaluated using a paired t-test. For the CGI-S, at each post-baseline assessment, a shift from baseline table summarizes the worsening, no change, and improvement relative to baseline. The PSP score was divided into categories based on a 10-point scale and summarized categorically. The shifts from baseline in the 10-point scale were also summarized and a shift to a higher score represented improvement. The PSP score is also presented using the following 3 categories to describe functionality: (1) Score of 1 to 30, requiring intensive support or supervision; (2) Score of 31 to 70, varying degrees of disability; (3) Score of 71 to 100, only mild difficulties. Frequency counts, percentages, and cumulative percentages along with a shift table summarizing changes relative to baseline were listed for these 3 PSP score categories.

For the RDQ, ready for discharge (yes/no) for hospitalized patients at each visit was treated as a binary outcome variable. The frequency, percentage, and cumulative percentage of ready for discharge were summarized by visit (time point) and at the end point. Time-to-readiness for discharge was calculated as the difference between the first visit date where the subject was indicated as ready for discharge and the date of the first dose of the study drug. Time-to-readiness for discharge was analyzed using Kaplan-Meier methodology. Hospitalized patients who did not meet criteria for readiness for discharge were censored at the time of withdrawal or completion of the study. The following Kaplan-Meier statistics and their corresponding 95% CIs were calculated: 25th percentile, median, and 75th percentile. In addition, the Kaplan-Meier curve for time-to-readiness for discharge was plotted. The hazard ratio for readiness of discharge was calculated by Cox proportional hazards regression methods. The Cox regression model

included as covariates the variables of age, gender, country, and PANSS total score at baseline, but was not limited to these variables.

The rate of drug discontinuation was summarized by the number and percentage of subjects who were discharged from hospital. The duration (length) of hospitalization was calculated. Time to first actual discharge from hospital was presented using the Kaplan-Meier methodology and was analyzed using the same Cox proportional hazards regression model as specified for the RDQ analysis.

RESULTS

STUDY POPULATION

A total of 212 subjects in the Asia Pacific region were enrolled from the following 4 countries: China (46.2%), Korea (22.6%), Taiwan (19.8%), and Malaysia (11.3%). Subjects had a mean (SD) age of 37.1 (11.8) years and 51% were men and 49% were women. Body weight was normal in 69.7% of subjects. All subjects had a diagnosis of schizophrenia (paranoid type, 70%). Duration of schizophrenic illness was ≤3 years for 60 (28%) subjects and >3 years for 152 (72%) subjects.

At enrollment, subjects had been acutely hospitalized with an exacerbation of schizophrenia for a mean (SD) duration of 38 (27.47) days. Subjects were moderately symptomatic reflected by a mean (SD) baseline PANSS score of 90.0 (17.41) and a score of ≥70 for 189 (89.2%) of subjects. The baseline mean (SD) PSP scale score was 42.8 (13.14) indicating poor functioning. The baseline mean (SD) CGI-S score was 4.9 (0.79) with 46.2% of subjects markedly ill. A total of 79.2% of subjects were treated with oral antipsychotic medications within the 6 months prior to the first study treatment and 74.1% of subjects were taking 1 or more psychotropic medications at baseline.

One hundred fifty-two (71.7%) subjects completed the study and 60 (28.3%) subjects withdrew prematurely: 4 (1.9%) subjects at Day 4, 7 (3.3%) subjects at Week 1, 22 (10.4%) subjects at Week 5, 18 (8.5%) subjects at Week 9, and 9 (4.2%) subjects at Week 13. The most common reason for study withdrawal was withdrawal of consent (24 subjects [11.3%]). Additional reasons for withdrawal from the study in >5% of subjects were lack of efficacy (13 subjects [6.1%]), which also included 3 subjects who experienced an AE that resulted in withdrawal from the study, and AEs (10 subjects [4.7%]).

One or more major protocol deviations were recorded for 33 (15.6%) subjects. The most common deviations were noted in the categories of ‘received excluded concomitant treatment’ (19 [9.0%] subjects) and ‘other’ (15 [7.1%] subjects).

EXPOSURE TO STUDY DRUG

A total of 161 (75.9%) subjects received all 4 study injections (83% in the recently diagnosed subgroup and 73% in the chronically ill subgroup). The mean [SD] dose of injection received by all subjects was 122.0 (13.63) mg eq. (mean of 120.3 mg eq. in the recently diagnosed and 122.7 mg eq. in the chronically ill subgroup). The median dose of injection was 112.5 mg eq. for all subjects in the recently ill subgroup and 120.8 mg eq. in the chronically ill subgroup.

In an analysis of the average mode dose (defined as dose with highest frequency; most frequent dose of injection) received by all subjects, the mean (SD) was 121.5 (26.8) mg eq. and was similar between the recently diagnosed subgroup, 115.8 (26.0) mg eq., and the chronically ill subgroup, 123.7 (26.9) mg eq.

The average (mean [SD]) dose of injection received by all subjects (N=180) based on third or later injection was 114.5 (25.5) mg eq. (110.9 mg eq. in the recently diagnosed and 116.8 mg eq. in the chronically ill subgroup).

One hundred sixty-one (75.9%) subjects received all 4 paliperidone palmitate injections. The duration of exposure for 49% of subjects was in the range of 64 to 91 days. Approximately 30% of subjects had

duration of exposure ≥92 days. Of the 90 subjects that required a dose adjustment, the majority of adjustments (78.9%) were due to insufficient efficacy.

The fourth (last) dose of study agent was 100 mg eq. for 120 subjects (56.6%), 150 mg eq. for 77 subjects (36.3%), and 75 mg eq. for 15 subjects (7.1%). The dose for the third injection (flexible dose) was 100 mg eq. for 105 subjects (58.3%), 150 mg eq. for 57 subjects (31.7%), and 75 mg eq. for 18 subjects (10.0%). Concomitant psychotropic medications were used by 182 (85.8%) subjects (oral atypical antipsychotics by 59 [27.8%] subjects and oral typical antipsychotics by 13 [6.1%] subjects). The number of subjects taking at least one concomitant psychotropic medication after Day 1 was 145 (68.4%).

EFFICACY

The efficacy analysis presented is based on the ITT analysis set (N=212) and included all subjects who received at least 1 dose of the study agent (or any portion of dose), regardless of their compliance with the protocol. The primary efficacy endpoint analysis of the mean (SD) change in PANSS total score from baseline to Week 13 last observation carried forward (LOCF) was -23.9 (23.24) and statistically significant for within group difference (p<0.001) and clinically meaningful improvement (95% CI= -27.10 to -20.78); the corresponding null hypothesis was rejected. The PANSS mean (SD) total score at study end point (Week 13 LOCF) was 65.8 (23.09), representing significant improvement from the baseline mean (SD) of 90.0 (17.41).

Positive and Negative Syndrome Scale (PANSS) Total Score: Change from Baseline to End Point (ITT Analysis)

Time point	Recently Diagnosed (≤3 years)		Chronically Ill (>3 years)		All Subjects	
Value	Actual	CFB	Actual	CFB	Actual	CFB
Baseline						
N	60		152		212	
Mean (SD)	89.4 (13.25)		90.2 (18.83)		90.0 (17.41)	
95% CI	(85.94, 92.79)		(87.20, 93.24)		(87.62, 92.33)	
Median	86.0		89.5		88.5	
Range	(68; 120)		(48; 190)		(48; 190)	
Day 4 LOCF						
N	60	60	148	148	208	208
Mean (SD)	80.7 (16.11)	-8.7 (9.60)	84.4 (19.68)	-5.1 (8.96)	83.3 (18.76)	-6.1 (9.27)
95% CI	(76.50, 84.83)	(-11.18, -6.22)	(81.19, 87.58)	(-6.52, -3.61)	(80.75, 85.88)	(-7.38, -4.85)
Median	81.0	-6.5	84.0	-4.0	82.5	-4.0
Range	(36; 121)	(-44; 2)	(42; 191)	(-47; 20)	(36; 191)	(-47; 20)
p-value[a]		<0.001		<0.001		<0.001
p-value[b]		<0.001		<0.001		<0.001
Week 13 LOCF						
N	60	60	150	150	210	210
Mean (SD)	58.0 (18.30)	-31.4 (18.19)	68.9 (24.10)	-21.0 (24.40)	65.8 (23.09)	-23.9 (23.24)
95% CI	(53.27, 62.73)	(-36.06, -26.67)	(65.05, 72.82)	(-24.90, -17.03)	(62.67, 68.95)	(-27.10, -20.78)
Median	57.0	-33.0	65.0	-19.0	62.0	-23.0
Range	(30; 113)	(-73; 15)	(35; 193)	(-94; 64)	(30; 193)	(-94; 64)
p-value[a]		<0.001		<0.001		<0.001
p-value[b]		<0.001		<0.001		<0.001

[a] p-values for within group difference are based on a paired t-test.
[b] p-values for within group difference are based on a Wilcoxon signed-rank test.

For the PP population (N=179) primary efficacy endpoint, the mean (SD) change in PANSS total score from baseline to Week 13 LOCF was -22.4 (23.28). The findings were consistent with the overall ITT analysis.

For the post hoc confirmatory analysis of efficacy (N=148 subjects), which excluded all subjects who had received an antipsychotic medication after Day 1 (n=64 subjects), the mean (SD) change in PANSS total score from baseline to Week 13 LOCF was -21.9 (23.51) and the 95% CI was -25.74 to -18.05 ($p<0.001$). The findings were consistent with the overall ITT analysis.

The PANSS responder rate (percentage of subjects with at least a 30% reduction from baseline in the PANSS total score at end point) was 63.8% (134/210 subjects) at Week 13 LOCF.

CGI-severity showed improvement at Week 13 LOCF with a mean (SD) change in score of -1.4 (1.33), which was statistically significant for within group difference ($p<0.001$) (95% CI = -1.61 to -1.25).

PSP showed improvement at Week 13 LOCF with a mean (SD) increase from baseline of 18.8 (17.56), which was statistically significant for within group difference ($p<0.001$) (95% CI=16.29−21.40).

One hundred forty-four (68%) subjects were discharged from the index hospitalization (defined as the hospitalization at the time of enrollment into the study). The median time to actual discharge was 37 days (95% CI=28 to 42 days) for all subjects and 35 days (95% CI=20 to 38 days) for the recently diagnosed subgroup and 41 days (95% CI=28 to 51 days) for the chronically ill subgroup.

The duration (days) of index hospitalization for all subjects was a mean (SD) of 38.0 (27.47) days with the majority of subjects (n [%]) in the range of 29 to 56 days (55 [25.9%]) and 57 to 91 days (54 [25.5%]), followed by 8 to 14 days (40 [18.9%]), and 15 to 28 days (38 [17.9%]).

One hundred sixty-five (77.8%) of subjects were ready for hospital discharge. Median time to ready for hospital discharge (days since first injection) was 35 days for both the chronically ill and recently diagnosed subgroups.

At the end of the study fewer subjects (21.7%, 13/60) in the recently diagnosed subgroup were in the hospital than in the chronically ill subgroup (36.2%; 55/152). Post-baseline psychiatric re-hospitalizations in the chronically ill subgroup (n=7) were slightly more than the recently diagnosed subgroup (n=1) and of longer duration (41 days vs. 13 days).

SAFETY

Overall Summary

One hundred thirty-nine (65.6%) subjects experienced one or more TEAEs of which 94 (44.3%) subjects experienced a TEAE that was possibly-related to treatment. No deaths occurred in the study. Fourteen (6.6%) subjects experienced a serious TEAE of which 4 subjects had serious ‘probably related’ TEAEs (schizophrenia, 1 subject, and sinus bradycardia, 3 subjects). TEAEs leading to treatment discontinuation were reported for 13 (6.1%) subjects (of which 3 subject discontinuations were identified by the investigator as lack of efficacy). For the AEs of clinical interest, extrapyramidal symptom AEs were reported for 37 (17.5%) subjects, prolactin-related AEs were reported for 29 (13.7%) subjects and a glucose-related (diabetes mellitus) AE was reported for 1 subject.

Safety Evaluation

TEAEs were experienced by 65% of subjects and occurred more frequently in the SOCs of investigations (15.1%), nervous system disorders (13.7%), infections and infestations (13.2%), and gastrointestinal disorders (11.3%). The most frequently reported AEs overall were constipation (9%), nasopharyngitis (8.5%), blood prolactin increased (8.5%), and insomnia (8%).

Most TEAEs were mild (57 [26.9%] subjects) to moderate (63 [29.7%] subjects) in severity and were more prevalent in the chronically ill subgroup (9.9%) than in the recently diagnosed subgroup (6.7%). Severe AEs were reported in 19 (9.0%) subjects and were mainly due to sinus bradycardia, infection, increased prolactin level, and psychiatric disorders.

TEAEs leading to treatment discontinuation occurred in thirteen (6.1%) subjects (11 [7.2%] subjects in the chronically ill subgroup and 2 [3.3%] subjects in the recently diagnosed subgroup). Of the 13 AEs leading to treatment discontinuation, 7 AEs were drug class effects and deemed related to treatment by the investigator: 4 subjects had sinus bradycardia, 1 subject had extrapyramidal symptoms (EPS), 1 subject had skin rash, and 1 subject had suicidal thoughts.

Of the related TEAEs, 17% were possible, 16.5% were probable, and 10.8% were very likely. TEAEs not related to study agent occurred in 33 (15.6%) subjects and AEs doubtful related occurred in 12 (5.7%) subjects.

Action taken as a result of TEAEs, was 'dose not changed' in 51% of subjects, 'drug withdrawn' in 6.1% of subjects, and 'not applicable' in 6.6% of subjects. One subject had action taken of 'dose increased' and 1 subject had 'dose reduced'. More subjects had dose withdrawn in the chronically ill (7.2%) than in the recently diagnosed (3.3%) subgroup.

Fourteen (6.6%) subjects reported 1 or more serious TEAEs and these occurred most frequently in the system organ class (SOC) of psychiatric disorders (8 [3.8%] subjects). The most frequently reported serious TEAE was schizophrenia in 7 (3.3%) subjects followed by sinus bradycardia in 3 (2.0%) subjects, both occurring more frequently in the recently diagnosed subgroup.

Four subjects had treatment-related serious TEAEs. The serious TEAE preferred terms were sinus bradycardia (3 subjects, probably related) and schizophrenia (1 subject; possibly related, verbatim term was aggravation of schizophrenia).

Extrapyramidal symptom (EPS) TEAEs were reported for 37 (17.5%) subjects and included the preferred terms of tremor (5.2), akathisia (4.7%), extrapyramidal disorder (3.3%), and dystonia (2.4). More EPS-related AEs were reported in the recently diagnosed subgroup (26.7%) than in the chronically ill subgroup (13.8%). No EPS AEs were serious or severe.

Adverse events related to blood glucose levels were reported for 1 subject in the chronically ill subgroup and the preferred term was diabetes mellitus. Adverse events related to blood prolactin level were reported for 29 (13.7%) subjects.

Hyperprolactinemia (25 [11.8%] subjects) was the most commonly reported preferred term and occurred with similar frequency between the recently diagnosed (10.0%) and the chronically ill (12.5%) subjects. No AE related to blood prolactin level led to study drug discontinuation or evolved into a serious AE. The incidence of hyperprolactinemia by gender was similar for men and women (5.7% vs. 6.1%, respectively).

Five subjects in the chronically ill subgroup had a clinically notable instance of increased pulse rate. A total of 14.6% of all subjects had weight gain of ≥7%, occurring more frequently in the recently diagnosed subgroup (20%) than in the chronically ill subgroup (12.5%). For subjects with normal body mass index (BMI), 17% increased by ≥7% at Week 13 LOCF of which more subjects were in the recently diagnosed subgroup (23%) than the chronically ill subgroup (13.6%).

STUDY LIMITATION(S)

The limitations of this study were its open-label design and lack of comparator group to better assess the efficacy evaluation and confounding variables.

CONCLUSION(S)

Paliperidone palmitate was efficacious in hospitalized Asian patients who had a recent exacerbation of acute schizophrenia within the 4 weeks prior to enrollment. Significant improvements were observed in psychotic symptoms, social functioning, and severity of illness. Paliperidone palmitate was well-tolerated and generally safe, demonstrating consistency with the known safety profile and without new safety signals.