

SYNOPSIS

<u>Name of Sponsor/Company</u>	Janssen Scientific Affairs, LLC
<u>Name of Finished Product</u>	INVEGA SUSTENNA®
<u>Name of Active Ingredient(s)</u>	R092670 (paliperidone palmitate)

Status: Approved
Date: 10 March 2014
Prepared by: Janssen Scientific Affairs, LLC

Protocol No.: R092670-SCA-3004

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Paliperidone Palmitate Evaluating Time to Relapse in Subjects With Schizoaffective Disorder

Study Name: PRIME

EudraCT Number: 2009-017271-17

NCT No.: NCT01193153

Clinical Registry No.: CR016618

Coordinating Investigator: David Walling, PhD, [REDACTED]; United States of America

Study Centers: Subjects were enrolled from 31 sites in the United States, 19 sites in Romania, 14 sites in India, 13 sites in the Ukraine, 6 sites in Bulgaria, 3 sites in Malaysia, 4 sites in the Philippines, and 5 sites in the Republic of South Africa

Publication (Reference):

Fu, DJ, Turkoz, I, Simonson RB, et al. Paliperidone Palmitate Long-Acting Injectable in Acute Exacerbation of Schizoaffective Disorder. Schizophrenia Bulletin.2013; 39 (Suppl 1):S331. 14th International Congress on Schizophrenia Research, April 21-25, 2013, Orlando, Florida.

Study Period: Study initiated 20 September 2010; Data base lock 25 November 2013; Study Completed 22 October 2013

Phase of Development: Phase 3b

Objectives:

Primary Objectives: The primary objectives of this study were to evaluate the efficacy of paliperidone palmitate compared with placebo in the delay of relapse of the symptoms of schizoaffective disorder and to assess the safety and tolerability of paliperidone palmitate in subjects with schizoaffective disorder.

Key Secondary Objective: The key secondary objective of this study was to evaluate change in subject functioning using the Personal and Social Performance Scale (PSP) during the double-blind Relapse Prevention period with paliperidone palmitate compared with placebo.

Other Secondary Objectives: The secondary objectives of this study were:

- To evaluate symptom change as measured by the Positive and Negative Syndrome Scale (PANSS) total and PANSS factor scores during the double-blind Relapse Prevention period with paliperidone palmitate compared with placebo
- To evaluate illness severity change as measured by Clinical Global Impression of Severity for Schizoaffective Disorder (CGI-S-SCA) during the double-blind Relapse Prevention period with paliperidone palmitate compared with placebo
- To evaluate change in subject medication satisfaction using the Medication Satisfaction Questionnaire (MSQ) during the double-blind Relapse Prevention period with paliperidone palmitate compared with placebo
- To evaluate change in mood symptoms as measured by Young Mania Rating Scale (YMRS), Hamilton Rating Scale for Depression, 21-item version (HAM-D-21), and HAM-D, 17-item version (HAM-D-17; the first 17 items from the HAM-D-21) during the double-blind Relapse Prevention period with paliperidone palmitate compared with placebo
- To explore the consistency of treatment effect across subjects receiving paliperidone palmitate as monotherapy and as an adjunct to mood stabilizers or antidepressants during the double-blind Relapse Prevention period
- To explore symptom change (ie, PANSS, YMRS, HAM-D-21, HAM-D-17), illness severity (CGI-S-SCA), subject functioning (PSP) and medication satisfaction (MSQ) with paliperidone palmitate during the Lead-in and Stabilization periods
- To explore the overall healthcare resource utilization using the Resource Utilization Questionnaire (RUQ) during the double-blind Relapse Prevention period with paliperidone palmitate compared with placebo
- To evaluate and explore genetic markers associated with paliperidone efficacy, safety and tolerability

Methodology: This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, international study to evaluate the efficacy and safety of paliperidone palmitate, as monotherapy or as an adjunct to mood stabilizers or antidepressants, relative to placebo in delaying the time to relapse in subjects with schizoaffective disorder. The study consisted of 4 periods: Screening (up to 7 days), Lead-in (13 weeks), Stabilization (12 weeks), and Relapse Prevention (15 months).

Screening Period: During screening eligibility was assessed based on the inclusion and exclusion criteria. Subjects without previous exposure to paliperidone palmitate, INVEGA[®] (ie, paliperidone extended-release [ER]), risperidone, or RISPERDAL CONSTA[®], were required to undergo an oral tolerability test (oral INVEGA 6 mg/day for 4 to 6 days). Only subjects who demonstrated an ability to tolerate the drug, as judged by the treating physician, were eligible for enrollment. Subjects could be inpatients or outpatients at the time of screening.

Lead-in Period: During the open-label, flexible-dose Lead-in Period, all subjects were treated with paliperidone palmitate for 13 weeks. Subjects received paliperidone palmitate either as monotherapy or as adjunct to mood stabilizers or antidepressants. The first dose of paliperidone palmitate was 234 mg (150 mg eq.) given on Day 1. The second dose of paliperidone palmitate was 156 mg (100 mg eq.) given on Day 8. Doses at Day 36 (Week 5), Day 64 (Week 9) and Day 92 (Week 13) were maintained, increased, or decreased in stepwise changes within the range of 78 mg (50 mg eq.) and 234 mg (150 mg eq.) as clinically indicated. Subjects could receive study medication within a ± 4 day window for the Day 8 injection and a ± 7 day window starting with the Day 36 injection.

Stabilization Period: Subjects who completed the Lead-in Period of the study and who meet defined stabilization criteria (PANSS total score ≤ 70 , and YMRS and HAM-D-21 ≤ 12 at the end of the Lead-in Period) entered the Stabilization period. During the 12-week Stabilization period, subjects were given paliperidone palmitate intramuscular (IM) injections once every 4 weeks (ie, on Day 120 and Day 148) at

the final dose received during the Lead-in period on Day 92 (Week 13). Subjects who completed the Stabilization period and maintained the stabilization criteria throughout the 12-week treatment were randomized into the double-blind Relapse Prevention period. Subjects who do not meet the predefined stabilization criteria were withdrawn from the study.

Relapse Prevention Period: After completing the 12-week Stabilization period, on Day 176 (Week 25), subjects who were eligible to enter the double-blind Relapse Prevention period were randomized in a 1:1 ratio to receive either a fixed dose of paliperidone palmitate or matching placebo. Randomization was stratified by the absence or presence of mood stabilizers or antidepressants and study center. The dosage of study drug was to remain unchanged from the dosage administered on Day 92. Subjects received study drug once every 4 weeks until one of the following occurred: 1) they met the prospectively defined relapse criteria; 2) they discontinued treatment for a reason other than relapse; 3) they withdrew consent; 4) they were lost to follow-up; or 5) they completed 15 months of double-blind treatment.

Number of Subjects (planned and analyzed): **Planned:** To meet the expected number of 286 subjects (143 per group) randomized in the double-blind Relapse Prevention period, a total of at least 520 subjects were to be enrolled in the open-label Lead-in period.

Analyzed: A total of 921 subjects were screened, 667 subjects were enrolled in the open-label Lead-in period, and 432 subjects entered the open-label Stabilization period. Of the 432 subjects who entered the open-label Stabilization period, 334 subjects were randomized to the double-blind Relapse Prevention period (170 subjects to the placebo group and 164 subjects to the paliperidone palmitate group).

Diagnosis and Main Criteria for Inclusion: Subjects were men and women ≥ 18 years of age. Subjects were to have had a lifetime and current diagnosis of schizoaffective disorder (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV] 295.70), as confirmed by the Structured Clinical Interview for DSM-IV Disorders (SCID) at screening. Subjects must have been experiencing an acute exacerbation of psychotic symptoms no less than 4 days and no more than 4 weeks in duration prior to screening. At screening, subjects were to have had a score of ≥ 4 on at least 3 of the following 9 PANSS items: Delusions (P1), Conceptual Disorganization (P2), Hallucinatory Behavior (P3), Excitement (P4), Suspiciousness/Persecution (P6), Hostility (P7), Tension (G4), Uncooperativeness (G8), and Poor Impulse Control (G14). Subjects were also to have had a score of ≥ 16 on YMRS **and/or** a score of ≥ 16 on the HAM-D-21 at screening.

To be eligible for randomization to the double-blind Relapse Prevention period, subjects were required to have a PANSS total score ≤ 70 , and YMRS and HAM-D-21 ≤ 12 at each visit during the 12-week Stabilization period. A single excursion in mood symptoms (YMRS and/or HAM-D-21 between 13 and 17 and not requiring hospitalization) was permitted during the first 8 weeks of the Stabilization Period. After such an excursion, the subject was to be brought in for an unscheduled visit and re-evaluated within 7 days and was required meet stabilization criteria for mood symptom ratings.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone palmitate prefilled syringes (78, 117, 156 and 234 mg, or 50, 75, 100, and 150 mg eq.) were provided by the sponsor for use during the open-label Lead-in, Stabilization, and double-blind Relapse Prevention periods.

Reference Therapy, Dose and Mode of Administration, Batch No.: Matching placebo injections (20% Intralipid [200 mg/mL] injectable emulsion) were provided during the double-blind period.

Duration of Treatment: During the open-label Lead-in period, subjects received paliperidone palmitate for a total of 13 weeks. Subjects who entered the open-label Stabilization period received paliperidone palmitate for an additional 12 weeks. Subjects randomized to the double-blind Relapse Prevention period received either placebo or paliperidone palmitate for up to 15 months.

Criteria for Evaluation: The primary efficacy end point for this study was the time between subject randomization to treatment and the first occurrence of a relapse during the Relapse Prevention period.

Relapse was defined as the first occurrence of ANY ONE of the following:

- Psychiatric hospitalization due to worsening symptoms (including ER visit ≥ 23 hours, and not including hospitalizations for social reasons)
 - Any intervention employed to avert imminent hospitalization due to worsening symptoms (eg, increase in the level of psychiatric care from office visit to day hospitalization [not including increased level of care for social reasons], or need for additional antipsychotic, antidepressants, or mood stabilizing medication)
 - Deliberate self-injury, suicidal or homicidal ideation that is clinically significant as determined by the investigator, or violent behavior resulting in clinically significant injury to another person or property damage
 - Worsening of any one or more of the following PANSS items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P4 (Excitement), P6 (suspiciousness/persecution), P7 (hostility), G8 (uncooperativeness), or G14 (Poor Impulse Control) to a score of ≥ 6 after randomization if the score on the corresponding item was ≤ 4 at randomization
 - Worsening, as specified below, in any of the following measures at two consecutive visits. The second confirmation assessment was to be made within 7 days of the initial assessment identifying the worsening score:
 - An increase of $\geq 25\%$ in total PANSS score from randomization if the score at randomization was > 45
 - A ≥ 10 points increase in total PANSS score from randomization if the score at randomization was ≤ 45
 - Worsening of any one or more of the following PANSS items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P4 (Excitement), P6 (suspiciousness/persecution), P7 (hostility), G8 (uncooperativeness), or G14 (Poor Impulse Control) to a score of ≥ 5 after randomization if the score on the corresponding item was ≤ 3 at randomization
 - Increase in CGI-S-SCA overall score
 - Increase of ≥ 2 points if the score at randomization was 1 (not ill) to 3 (mildly ill)
- OR
- Increase of ≥ 1 point if the score at randomization was ≥ 4 (moderately ill or worse)

Safety evaluations for this study included the monitoring of adverse events, clinical laboratory tests, electrocardiograms (ECGs), vital sign measurements (temperature, pulse, and blood pressure), weight, and the monitoring of extrapyramidal symptoms using the Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A). Suicidality was assessed by the Columbia Suicide Severity Rating Scale (C-SSRS).

Statistical Methods: Efficacy and safety summaries for the open-label periods were based on the open-label intent to treat (ITT) analysis set, which included all subjects who received at least one injection of open-label study drug. Efficacy and safety summaries for the double-blind Relapse Prevention period of the study were based on the double-blind ITT analysis set which included all randomized subjects who received at least one injection of double-blind study medication. The primary population for efficacy was the double-blind ITT analysis set.

Efficacy analyses: The primary efficacy end point for this study was the time between Day 1 of the double-blind period and the first documentation of a relapse during the Relapse Prevention period. The primary efficacy null hypothesis was that there is no difference in the distribution of time to relapse between the paliperidone palmitate and placebo groups in subjects with schizoaffective disorder.

Treatment differences were compared using a log-rank test stratified by concomitant medication stratum (treatment with mood stabilizers or antidepressants or no such treatment). The cumulative distribution function of the time to relapse was estimated by the Kaplan-Meier method. The 95% confidence intervals (CIs) for the median relapse rates, as well as the relapse rates at 3 months, 6 months, 9 months, 1 year, and at 15 months were provided. Standard Error (SE) estimates were based on Greenwood's formula. The reasons for relapse were summarized at each visit and end point. Risk of relapse for the subgroup of subjects on monotherapy, adjunctive therapy, antidepressants, and mood stabilizers were also examined using Cox proportional hazard models. Whether or not the overall observed risk ratio of relapse between treatment groups differs among the mood episode types was also examined.

For the double-blind Relapse Prevention period, PSP was a key secondary endpoint that was pre-specified in the statistical analysis plan (SAP). The key secondary efficacy variable is the mean change from double-blind baseline in PSP score at DB end point (Month 15). The corresponding null hypothesis for the key secondary endpoint was that there is no difference in mean change from double-blind baseline in the PSP score between paliperidone palmitate and placebo at end point.

The overall type I error rate for testing paliperidone palmitate versus placebo for both the primary efficacy endpoint and key secondary efficacy endpoint was controlled at the 2-sided 0.05 significance level using a fixed sequence gatekeeper approach. Time to first relapse was tested first, followed by change from baseline in PSP. If the null hypothesis corresponding to time to first relapse was rejected, then the PSP would be tested at the 5% level, thus maintaining an overall Type I error rate of 5%. If the primary null hypothesis was not rejected, testing of change from baseline in PSP will still be performed, but no unqualified statements about the statistical significance regarding change from baseline in PSP would be made.

The change from double-blind baseline in PSP score was analyzed using a mixed model repeated measures (MMRM) Analysis of Covariance (ANCOVA) model. Using this model, treatment effects at the Month 15 end point were estimated based on differences between least squares (LS) means. Accompanying 95% CIs for the LS mean differences between palmitate and placebo were presented. Additional, supportive, sensitivity analyses (pattern mixture model, tipping-point analysis, and pattern mixture modeling with multiple imputation) were performed to assess the robustness and consistency of findings at the Month 15 end point. Frequency counts, percentages, and cumulative percentages of subjects reporting each PSP deciles, PSP categories, and PSP domain levels were also summarized for both observed data and last observation carried forward (LOCF) data by treatment group. To evaluate the clinical relevance of the PSP results, supplementary analyses were conducted to examine subject level PSP data as a categorical endpoint as well as time to at least 7 points and 10 points decrements in PSP. The objective of these analyses was to provide a comprehensive assessment of the PSP scale in estimating clinically meaningful treatment differences at a subject level while still considering the problems of data missingness.

Changes in the other secondary efficacy end points (PANSS [total, factor scores, and subscales], HAM-D-21, YMRS, and CGI-S-SCA) from randomization to each visit and to the end point were analyzed using an analysis of covariance (ANCOVA) model using both Last Observation Carried Forward (LOCF) and observed cases. The model included treatment, concomitant medication stratum, and country as fixed-effect design factors, and corresponding baseline scale score as a covariate. Using this model, treatment effects were estimated based on differences between LS means. Accompanying 95% CIs for the LS mean differences were presented. The within-treatment-group difference for change from baseline was evaluated using a paired t-test. Plots of the mean change from baseline in PANSS total score, HAM-D-21, YMRS, and CGI-S-SCA were also presented by treatment group for both the observed and LOCF data.

The change from open-label baseline during the open-label treatment period for efficacy variables was summarized descriptively and examined using paired t-tests. These summaries were repeated for those

subjects who were on monotherapy and adjunctive therapy. No adjustments were made for multiplicity, as this period was used to determine acceptability for entry to the double-blind period.

Descriptive statistics of MSQ, and RUQ were presented for both periods and the efficacy analyses described above were repeated for each post-baseline assessment time point and LOCF.

Safety analyses: For each treatment group, adverse events, clinical laboratory results, vital signs, and ECGs were summarized by treatment group using descriptive statistics and listed for each subject at each measurement time point. Subjects who died are listed. Serious adverse events were summarized and individual subjects with serious adverse events are listed. Summaries for serious adverse events and discontinuations due to adverse events were generated separately for the open-label and double-blind treatment groups. The results of the ESRS-A were summarized using descriptive statistics and frequency counts on changes from open-label or double-blind baseline values. Suicidality data collected using C-SSRS were summarized descriptively for each period. In addition, for open-label subjects, switch-to-depression, worsening of preexisting depression, and de novo depression were evaluated.

RESULTS:

STUDY POPULATION:

A total of 667 subjects were enrolled into the open-label period, 347 subjects received paliperidone palmitate as adjunctive therapy to mood stabilizers or antidepressants and 320 subjects received paliperidone palmitate as monotherapy. Of the 667 subjects enrolled, 432 subjects entered the Stabilization period and 334 of these subjects were randomized in a 1:1 ratio to receive either placebo (170 subjects) or to continue receiving paliperidone palmitate (164 subjects) in the double-blind Relapse Prevention period.

The majority of subjects enrolled in the open-label period were white (53.1%). There were a higher percentage of male (53.5%) subjects than female (46.5%) subjects and the mean age was 39.5 years (range: 19 to 66 years). The demographic and baseline characteristics of the 334 subjects randomized to the double-blind Relapse Prevention period were similar to those described for subjects enrolled in the open-label period.

The most common reason for discontinuation among all open-label subjects was withdrawal of consent (14.7%). Additional reasons for discontinuation in >5% of subjects included adverse events (7.5%), failure of criteria to enter the Stabilization period (7.0%), loss to follow-up (6.3%), and failure of criteria to enter the double-blind Relapse Prevention period (5.2%). During the double-blind period, the most common reason for discontinuation in both the placebo and paliperidone palmitate groups was withdrawal of consent, 17.6% and 11.6%, respectively. A greater proportion of subjects in the paliperidone palmitate group (7.3%) discontinued the study due to an adverse event compared to subjects in the placebo group (1.8%).

EFFICACY RESULTS:

The primary efficacy end point for this study was the time between Day 1 of the double-blind period and the first documentation of a relapse during the double-blind Relapse Prevention period. A greater proportion of subjects in the placebo group (57 subjects [33.5%]) experienced a relapse compared to the paliperidone palmitate group (25 subjects [15.2%]). Continued treatment with paliperidone palmitate was associated with a significant delay in time to relapse compared with placebo ($p < 0.001$) using the log-rank test controlling for concomitant medication strata. The null hypothesis that there was no difference in the distribution of time to relapse between the two treatment groups was rejected. A significant delay in time to relapse of schizoaffective symptoms ($p < 0.001$) was observed for subjects in the paliperidone palmitate group compared with subjects in the placebo group using a log rank test without stratification for concomitant medication stratum.

Time to Relapse, Days

DB ITT Analysis Set (Study R092670-SCA-3004)

	Placebo	Pali Palmitate	All Double Blind
Time to Relapse, Days			
Number assessed	170	164	334
Relapsed	57 (33.5%)	25 (15.2%)	82 (24.6%)
Censored	113 (66.5%)	139 (84.8%)	252 (75.4%)
Kaplan-Meier Median, Days	-	-	-
(95% CI)	(-, -)	(-, -)	(-, -)
Kaplan-Meier 25th Percentile, Days	169	-	294
(95% CI)	(127, 273)	(-, -)	(219, -)
Kaplan-Meier 75th Percentile, Days	-	-	-
(95% CI)	(-, -)	(-, -)	(-, -)
Kaplan-Meier Estimate Probability of Relapse			
Month 3	0.13	0.08	0.10
(95% CI)	(0.08, 0.18)	(0.04, 0.12)	(0.07, 0.14)
Month 6	0.26	0.12	0.19
(95% CI)	(0.19, 0.32)	(0.07, 0.17)	(0.14, 0.23)
Month 9	0.32	0.14	0.23
(95% CI)	(0.24, 0.39)	(0.09, 0.20)	(0.18, 0.28)
Month 12	0.37	0.17	0.27
(95% CI)	(0.29, 0.45)	(0.11, 0.23)	(0.22, 0.33)
Month 15	0.39	0.17	0.28
(95% CI)	(0.31, 0.48)	(0.11, 0.23)	(0.23, 0.34)
Log-Rank p-value ^a	<0.001		
Log-Rank p-value ^b	<0.001		

Note: Percentages are based on the number of patients assessed in the DB ITT population.

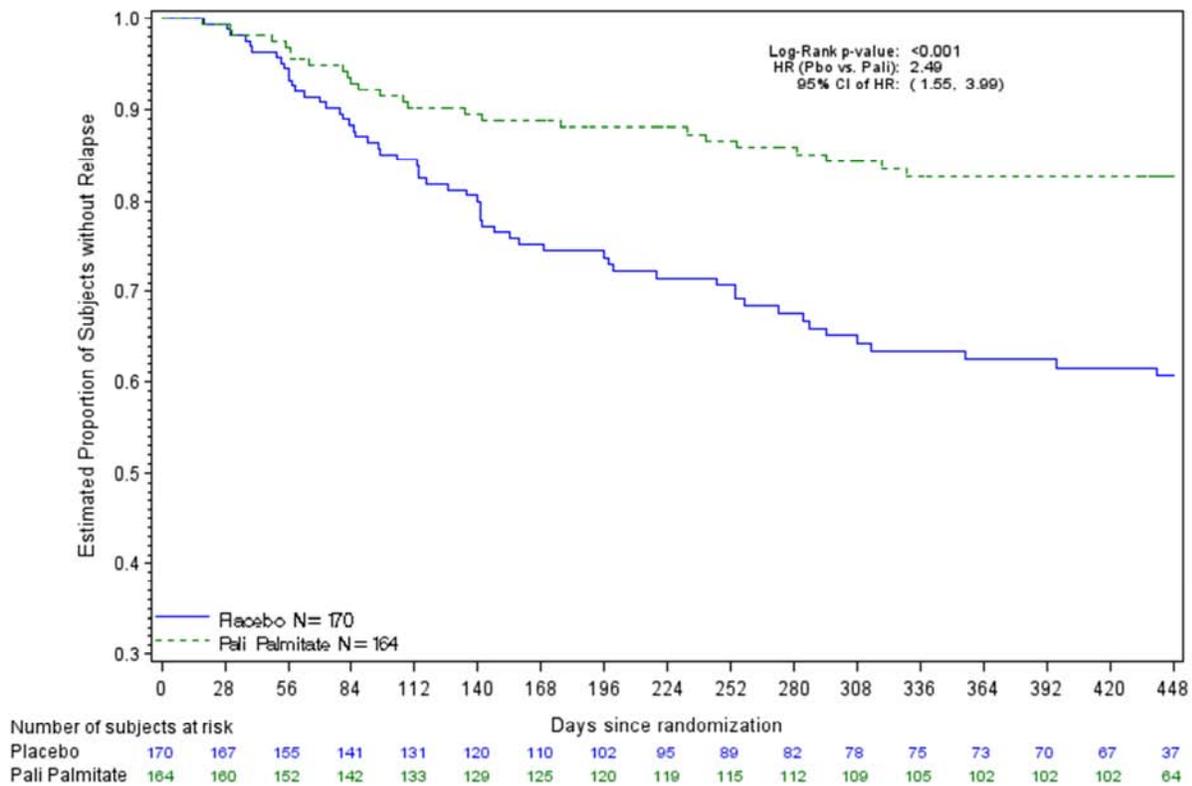
^a Primary efficacy evaluation. Log-Rank p-value compares all patients taking paliperidone palmitate vs. those taking placebo stratified by concomitant medication stratum.

^b Log-Rank p-value compares all patients taking paliperidone palmitate vs. those taking placebo.

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The risk of relapse was 2.49 (95% confidence interval [CI]: 1.55, 3.99; p<0.001) fold higher for a subject who was switched to placebo than for a subject who continued to receive paliperidone palmitate in the double-blind period.

Kaplan-Meier Plot of Time to Relapse, Days Analysis Set (Study R092670-SCA-3004)



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The most common reasons for relapse across both treatment groups were worsening of clinical scores at 2 consecutive visits and interventions employed to avert hospitalizations. A higher percentage of subjects in the placebo group (7.1%, n=12) than the paliperidone palmitate group (3.0%, n=5) were hospitalized for decompensating of the subjects' schizoaffective symptoms.

Analysis of the subgroup of subjects on adjunctive therapy and monotherapy demonstrated that the risk of relapse was 2.03 or 3.38 times greater with the placebo group in adjunctive antidepressant/mood stabilizer treatment or in monotherapy, respectively (hazard ratio (HR) 2.03; 95% CI 1.11-3.68; p=0.021 and HR 3.38; 95% CI 1.57-7.28; p=0.002).

In addition, the Cox proportional hazards model was extended to include 3 types of mood events determined by the investigators: manic, depressive and mixed. The risk of relapse due to mood symptoms was higher for subjects in the placebo group than for subjects continuing paliperidone palmitate treatment. Compared to subjects in the paliperidone group, the risk of relapse in the placebo group was 2.93 (95% CI: 1.70, 5.04; p<0.001) times higher for relapse due to any mood symptom; 3.62 (95% CI: 1.32, 9.89; p=0.012) times higher for relapse due to manic symptoms; 3.12 (95% CI: 1.39, 6.98; p=0.006) times higher for relapse due to depressive symptoms; and 1.93 (95% CI: 0.65, 5.78; p=0.238) for relapse due to mixed symptoms. Test of hypotheses for any difference in event types was examined by the Global Competing Risk Test. The overall observed risk ratio of relapse in favor of paliperidone palmitate did not differ across types of mood episode, p=0.718.

The Cox proportional hazards model was also extended to relapses with psychotic symptoms as determined by the investigators. The risk of relapse due to psychotic symptoms was 2.82 (95% CI: 1.70-4.67; p<0.001) times higher for subjects in the placebo group than for subjects continuing paliperidone palmitate treatment.

Summary of Relapse Rates and Risk of Relapse (Hazard Ratios)

	Placebo Event/N (%)	Pali Palmitate Event/N (%)	Risk of relapse (Placebo vs. Pali Palmitate) ^a	p-value	95% CI of Risk of Relapse
All Subjects	57/170 (33.5%)	25/164 (15.2%)	2.49	<0.001	(1.55, 3.99)
Monotherapy	24/73 (32.9%)	9/78 (11.5%)	3.38	0.002	(1.57, 7.28)
Adjunctive to Antidepressants or Mood Stabilizers	33/97 (34.0%)	16/86 (18.6%)	2.03	0.021	(1.11, 3.68)
Psychotic Symptoms ^b	53/170 (31.2%)	21/164 (12.8%)	2.82	<0.001	(1.70, 4.67)
Mood Symptoms ^c					
Any Mood Symptoms	48/170 (28.2%)	18/164 (11.0%)	2.93	<0.001	(1.70, 5.04)
Manic	16/170 (9.4%)	5/164 (3.0%)	3.62	0.012	(1.32, 9.89)
Depressive	23/170 (13.5%)	8/164 (4.9%)	3.12	0.006	(1.39, 6.98)
Mixed	9/170 (5.3%)	5/164 (3.0%)	1.93	0.238	(0.65, 5.78)

^a The instantaneous risk (hazard) of relapse for a placebo treated subjects compared to Paliperidone Palmitate treated subjects. Risk of relapse, corresponding p-values, and 95% CIs are from separate Cox proportional hazards regression models.

^b 8 subjects experienced a relapse without psychotic symptoms.

^c 16 subjects experienced a relapse without any mood symptom element.

The overall type I error rate for testing paliperidone palmitate versus placebo for both the primary efficacy endpoint and key secondary efficacy endpoint was controlled at the 2-sided 0.05 significance level, using a fixed sequence gatekeeper approach. Time to first relapse was tested first, followed by change from baseline in PSP (key secondary endpoint). There was a significant difference ($p=0.014$) between the 2 treatment groups when comparing the mean change from baseline at Month 15 using the MMRM approach. The null hypothesis that there was no difference in mean change from baseline in the PSP score between paliperidone palmitate and placebo at Month 15 end point was rejected. The LS Mean (95% CI) difference between the treatment groups in change scores at Month 15 was 3.3 (0.68, 5.95). To address the concern about missing PSP data and the validity of MAR assumption, additional statistical analyses were completed. Overall results from additional sensitivity analyses showed that paliperidone palmitate was superior to placebo in maintaining functioning as measured by the PSP scale at end point. To further evaluate the clinical relevance and consistency of the PSP results, subject level PSP data as a categorical endpoint as well as time to clinically significant decrements in PSP were examined. These additional PSP evaluations also supported the primary finding that paliperidone palmitate was superior to placebo in maintaining functioning.

For each of the additional secondary efficacy analyses of PANSS total score, HAM-D-21 score, YMRS score, and CGI-S-SCA overall score there was a statistically significant ($p<0.001$) difference between treatment groups (change from double-blind baseline to end point) in favor of paliperidone palmitate. There was a statistically significant ($p=0.010$) difference between treatment groups in favor of paliperidone palmitate on the patient reported outcome, Medication Satisfaction Questionnaire.

Additionally, statistically significant improvements from baseline were observed for all efficacy variables during the 25-week, open-label, flexible dose paliperidone palmitate treatment of subjects with schizoaffective disorder who were experiencing an acute exacerbation of the illness.

PHARMACOGENOMIC RESULTS: No prospective pharmacogenomic analyses were performed during this study.

SAFETY RESULTS:

Overall, 62.5% of the 667 subjects in the open-label period reported at least 1 treatment-emergent adverse event (TEAE). The most frequently reported adverse events coded to the Nervous System and Psychiatric Disorders SOCs, 29.8% and 21.9% of subjects, respectively. The most common TEAEs ($\geq 10\%$ of subjects) during the open-label period were akathisia (11.1%), injection site pain (10.6%), and insomnia (10.0%). A total of 50 subjects (7.5%) reported TEAEs that led to treatment discontinuation and 54 subjects (8.1%) experienced 1 or more serious adverse events. Three subjects died during the open-label period due to completed suicide, cardiogenic shock and coma, and myocardial infarction.

During the double-blind period, 55.9% of subjects in the placebo group and 64.6% of subjects in the paliperidone palmitate group reported at least 1 TEAE during the double-blind period. Treatment-emergent adverse events that occurred more frequently in the paliperidone palmitate group than the placebo group (a 2% difference or more between groups) were: weight increased (8.5% vs 4.7%), nasopharyngitis (5.5% vs 3.5%), headache (5.5% vs 3.5%), hyperprolactinaemia (4.3% vs 1.2%), and pyrexia (3.7% vs 1.2%). A greater proportion of subjects in the placebo group experienced a serious adverse event compared to subjects in the paliperidone palmitate group, 9.4% and 5.5%, respectively. Two subjects (both randomized to the paliperidone palmitate group) died during the double-blind period, one subject died of an overdose of sleeping pills and the second subject died of coronary artery disease.

Extrapyramidal symptom-related TEAEs were reported in 23.2% of all open-label subjects and led to the discontinuation of 6 subjects. In the double-blind period, extrapyramidal symptom-related TEAEs were reported by 8.5% of subjects in the paliperidone palmitate group compared to 7.1% of subjects in the placebo group. Glucose-related TEAEs were uncommon during both the open-label (6 subjects, 0.9%) and double-blind (2.4% and 1.8% of subjects in the placebo and paliperidone palmitate groups, respectively) periods.

The incidence of subjects in the open-label period with prolactin-related TEAEs was 10.0% for female subject and 9.0% for male subjects. Prolactin-related TEAEs led to the discontinuation of 9 subjects. In the double-blind period, prolactin-related TEAEs were reported by a greater proportion of subjects in the paliperidone palmitate group (female subjects [13.9%] and male subjects [7.1%]) than in the placebo group (female subjects [5.8%] and male subjects [1.2%]).

A total of 18.4% of open-label subjects had at least a 7% increase in their body weight at end-point open-label, a change that was consistent across the adjunctive therapy and monotherapy groups. For 8.5% of subjects, weight increased was spontaneously reported as an adverse event. None of the events were serious or led to study discontinuation. In the double-blind period a greater percentage of subjects in the paliperidone palmitate group (13.0%) had at least a 7% increase in their body weight compared to the placebo group (6.0%) at double-blind end point. For 8.5% of subjects in the paliperidone palmitate group and 4.7% of subjects in the placebo group, weight increased was spontaneously reported as a TEAE. None of the events were serious and only 1 subject in the paliperidone palmitate group discontinued due to a TEAE of weight increased.

STUDY LIMITATIONS:

- As is the case for most controlled studies for regulatory submission, the subject population was chosen to minimize confounding factors. Therefore the results may not be generalizable to all schizoaffective disorder patients in general psychiatric practice.
- The study had a fixed duration of a 15-month double-blind treatment. The findings presented may differ for other duration times.

- There was no comparator group for the open-label efficacy evaluation. However, the observed efficacy in acute treatment of psychosis and mood symptoms was similar to that of the previous 2 double-blind, placebo-controlled studies of paliperidone ER which were the basis for regulatory approval.

CONCLUSION(S): Paliperidone palmitate treatment at doses of 78 mg to 234 mg (50 mg eq. to 150 mg eq.) significantly delayed relapse in subjects with schizoaffective disorder. Paliperidone palmitate was effective in delay of relapse of the symptoms of schizoaffective disorder, as both monotherapy and adjunctive therapy to antidepressants or mood stabilizers. In addition, paliperidone palmitate treatment was effective in decreasing risk of relapse due to psychotic, manic and depressive mood symptoms. Furthermore, paliperidone palmitate was also effective in maintaining subject function. Results of the open-label period of this study suggested that paliperidone palmitate without oral supplementation reduced psychotic, manic and depressive mood symptoms as well as improved subject functioning in acute schizoaffective disorder when administered as both monotherapy and adjunctive therapy to antidepressants or mood stabilizers. The overall findings from this study demonstrated the long-term efficacy and safety of paliperidone palmitate in subjects with schizoaffective disorder.