SYNOPSIS

Name of Sponsor/Company	Janssen Cilag
Name of Finished Product	Sustenna™
Name of Active Ingredient(s)	R092670 (Paliperidone Palmitate)

* Janssen Cilag is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Cilag studies may vary.. The term "sponsor" is used to represent these various legal entities as identified on the Sponsor List.

Status: Final

Date: 12-May-2014

Prepared by: Janssen - Cilag SA de CV

Protocol No.: R092670SCH3012

Title of Study: Treatment of Patients With Recently Exacerbated Schizophrenia With Paliperidone Palmitate - A Pilot Study

NCT No.: 01448720

Clinical Registry No.: [CR017977, R092670SCH3012]

Study Centers: The study was conducted at 14 centers in three countries: Brazil 6 centers, Colombia 4 centers and Mexico 4 centers.

Publication (Reference): [None to date]

Study Period: September 3, 2011 to December 2, 2013.

Phase of Development: 3b.

Objectives: As this was an open-label, single-arm, pilot study, all objectives were exploratory.

Primary objective

☐ To explore the efficacy of paliperidone palmitate given once monthly, as measured by the percentage of subjects with schizophrenia with at least a 30% reduction from baseline in Positive And Negative Syndrome Scale (PANSS) total score over 4 months.

Secondary objectives

☐ To explore changes in the PANSS total score and PANSS sub-domains/symptom factors.

☐ To explore the effects on the level of functioning measured by the Personal and Social Performance (PSP) scale.

☐ To explore changes in global severity of illness using the Clinical Global Impression - Severity (CGI-S) scores.

Methodology: This was a non-randomized, open-label, multicenter study of paliperidone palmitate in an optimized dose regimen planned in approximately 150 subjects with an acute exacerbation of schizophrenia designed to explore the percentage of subjects with at least a 30% reduction from baseline in PANSS total score after its administration. Subjects must have been in early phase of schizophrenia defined as a period of at least 1 year, but no longer than 5 years since the diagnosis. The study consisted of 2 phases: an up to 4-day screening phase and a 4-month core treatment phase (injections were administered from Day 1 to Day 92 at specified visits followed by an end-of-study visit on Day 120) without an extension period.

Number of subjects (planned and analyzed): The planned sample size was of 150 subjects entering the study. The sample size was not based on any statistical calculations for power as this is an exploratory study, in the context of an open-label, single-arm investigation. There were 151 subjects enrolled, but only 144 were included in the safety analysis (intention-to-treat, ITT population) and 100 subjects in the efficacy analysis [evaluable, Per Protocol (PP)].

Diagnosis and main criteria for inclusion:

Subjects between 18 and 40 years otherwise healthy with acute exacerbation of schizophrenia [Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) for at least 1 year before screening and no longer than 5 years (early diagnosed subjects)] for less than 4 weeks, but more than 4 days, with a PANSS total score at screening of 70 to 120 (inclusive), and CGI-S score of 4 or more (at least moderately ill) at screening (baseline).

Any potential subject who met any of the following main criteria was excluded: evidence of clinically significant cardiovascular, renal, hepatic, gastrointestinal (including narrowing or blockage of their gastrointestinal tract), neurological, endocrine, metabolic or pulmonary disease in the past 6 months that would increase the risk associated with taking study medication or would confound the interpretation of the study; psychiatric diagnosis due to direct pharmacological effects of a substance or a general medical condition; history or current symptoms of tardive dyskinesia, neuroleptic malignant syndrome or hypersensitivity to risperidone or paliperidone or their excipients.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone palmitate was administered intramuscular (IM) as an initial loading dose of 150 mg eq. (234 mg) on Day 1 and 100 mg eq. (156 mg) on Day 8 (± 4 days) in the deltoid muscle. Although a dose of 75 mg eq. (117 mg) was recommended from Day 36 (± 7 days) until Day 92 (± 7 days), the study drug could be administered in additional available strengths of 50 mg eq. (78 mg), 100 mg eq., and 150 mg eq. at 1-month intervals as either deltoid or gluteal muscle injections at the investigator's discretion.

Batch no. NA.

Duration of Treatment: Three months of therapy and 1 month of follow-up.

Criteria for Evaluation: The primary endpoint of efficacy was the responder rate, defined as the percentage of subjects with at least a 30% reduction from baseline in the PANSS total score at endpoint. Response was analyzed at each time point including last observation carried forward (LOCF) endpoint. The cumulative response rate (percentage of subjects experiencing response at any time from baseline up to a specified time point), 20%, 40%, and 50% response rates -based on PANSS total score- and time to first response, expressed as number of days from the first injection date to first response, were studied. Treatment failure was evaluated by assessing psychiatric hospitalization, suicidal behavior, substantial clinical deterioration, as indicated by a score of 6 (severe) or 7 (extremely severe) on the CGI-S scale, and discontinuation of the study drug due to inadequate efficacy or due to safety or tolerability issues, as determined by the investigator. Safety was monitored by the evaluation of all treatment-emergent adverse events (TEAE) and serious adverse events (SAE). Evaluations were performed at Days 1, 4, 8, 36, 64, 92 and 120.

Statistical Methods:

The current sample size was not based on any statistical calculations for power as this was an exploratory study designed to obtain information on the response rates, mean, and variance of various efficacy measures following paliperidone palmitate administration once monthly in this subject population. A sample size of 150 subjects entering the study was deemed to be sufficient to allow for a preliminary exploration of safety and efficacy in this open-label, single-arm study.

Efficacy. Responder rates were calculated. Response was analyzed at each time point including LOCF endpoint. The number and percentage of subjects who met the definition of a responder was presented for the ITT and evaluable analysis sets. The cumulative response rate was analyzed. In addition to 30% response rates, 20%, 40%, and 50% response rates based on PANSS total score were summarized.

Confidence intervals at 95% (95% CIs) for the proportion of subjects that achieved at each point, at least a 30% reduction in PANSS total score with respect to baseline, were calculated, as well as the p-values for the test of hypothesis of H_0: p=0.35 *vs*. H_a: p>0.35. For the case of the proportion of subjects that achieved a 20%, 40% or 50% reduction on PANSS total score compared to baseline, 95% CIs were calculated. Percentage of change to evaluate response was calculated considering the appropriate adjustment that converts the scale to a ratio scale beginning in zero, while basic statistics of the raw percentage of change, as well of the adjusted percentage, were obtained. Time to first response (expressed as number of days from the first injection date to first response) was analyzed using Kaplan-Meier methodology. In addition, subjects with various response patterns including early responders, early persistent responders, non-persistent responders, and late responders were identified and summarized.

The actual values and changes from baseline (if appropriate) for the following continuous/ordinal efficacy variables were summarized descriptively for both, observed and LOCF data. The differences for change from baseline were evaluated using a paired t-test and 95% CIs for change scores were also be calculated as appropriate. These summaries and analyses were performed on both the ITT and PP analysis sets.

In addition, frequency counts, percentages, and cumulative percentages of subjects reporting each CGI-S, PSP and Medication Satisfaction Questionnaire (MSQ) score were summarized by each time point and at LOCF endpoint. Worsening or improvement in satisfaction evaluation was defined by a change of one or more level from visit 4 evaluation.

Safety and tolerability. Safety variables analyzed included AEs, SAEs and serious treatment-emergent safety events (SSEs) incidence, concomitant medications, scores on movement disorder measures, Abnormal Involuntary Movement Scale (AIMS), InterSePT Scale for Suicidal Thinking-Plus (ISST-Plus), laboratory parameters, vital signs (VS), and electrocardiogram (ECG) measures. The ITT analysis set was used for analyses performed on safety parameters.

RESULTS:

STUDY POPULATION: Total population consisted of 151 patients. Seven patients (4.6%) were excluded of analysis because they did not take the drug under study and were considered screen failure. Then, 144 patients made up the ITT population. Of them, 121 completed the study.

Further, 44 patients of the ITT population (30.6%) were excluded (22 cases for violations to inclusion/exclusion criteria, 23 cases lost in follow-up and 25 cases for non-compliance with drug) (some patients had two or more reasons). Finally, PP population consisted of 100 patients.

Mean age of ITT population was 26.8 ± 6.2 years. One hundred and one (70.1%) were males. Meanwhile, mean age of PP population was 26.4 ± 6.0 years. Seventy-four patients (74.0%) were males.

EFFICACY RESULTS: Data sets analyzed were by visit and by visit-LOCF of PP and ITT populations.

Primary efficacy endpoint: Percentage of subjects with at least a 30% reduction from baseline in PANSS total score over 4 months was 82.8% at visit 8, and 83.0% at LOCF endpoint, respectively. On both types of assessment points, there was statistical evidence to support that the proportion of subjects that achieved at least a 30% reduction in PANSS total score compared to baseline, was >35%, from visit 5 (PP and ITT populations). So, the central hypothesis of the study was supported.

Secondary efficacy endpoints: Key secondary efficacy results are summarized in the table (mean ± S.D.) below:

	Per Protocol Population (n=100)
PANSS total score (mean ± S.D.)	
Mean baseline score	93.7 ± 13.2
Mean change from baseline at LOCF endpoint	-34.5 ± 17.7*
PANSS general subscale score (mean ± S.D.)	
Mean baseline score	45.5 ± 7.5
Mean change from baseline at LOCF endpoint	-16.3 ± 9.7*
PANSS positive subscale score (mean ± S.D.)	
Mean baseline score	22.6 ± 4.7
Mean change from baseline at LOCF endpoint	-11.4 ± 6.3*
PANSS negative subscale score (mean ± S.D.)	
Mean baseline score	25.6 ± 5.8
Mean change from baseline at LOCF endpoint	-6.8 ± 6.2*
PSP total score (mean ± S.D.)	
Mean baseline score	48.2 ± 14.1
Mean change from baseline at LOCF endpoint	16.4 ± 16.0*
CGI-S score (mean ± S.D.)	
Mean baseline score	4.8 ± 0.6
Percentage of patients that improved the CGI-S score in one grade or more, with respect to baseline at LOCF endpoint	92.0%

*p<0.0001 *versus* baseline (paired t-test)

- Statistically significant changes from baseline, on all visits and LOCF assessment points, in the PANSS total score and PANSS sub-domains/symptom factors occurred toward improvement in all sub-domains and symptom factors (p<0.001 for all analysis, paired T- tests) (Tables 3-6). Thus, PANSS total (raw score) on evaluation by visit, initially was 93.7 ± 13.2 and at 4 months, improved to 59.3 ± 14.8. PANSS total (raw score) on visit-LOCF endpoints, started at 82.1 ± 15.8 (Visit 4-LOCF) and finished at 59.2 ± 14.8 points (LOCF endpoint).

- Similarly, level of functioning measured by the Personal and Social Performance (PSP) scale improved significantly, since paired T-tests comparing each post-baseline point and visit-LOCF assessments to baseline, showed evidence of significant differences (p<0.001, paired t-tests). On the other hand, 95% CIs of the mean PSP score (Tables 10 and 11) showed no overlapping from visit 5 (Month 1) on, with baseline interval, on PP population; no overlapping of 95% CIs also occurs on visit-7 LOCF and LOCF endpoint, on this population. Similar results are observed for ITT population.

- The CGI-S score (Tables 44 and 45) used to evaluate global severity of illness showed statistically significant improvement compared to baseline. CGI-S changed from 4.8 ± 0.6, at baseline, to 3.1 ± 0.9 (month 4), while the LOCF assessment revealed a score of 4.4 ± 0.8 at visit 4-LOCF, and of 3.1 ± 0.9 at LOCF endpoint, on PP population. Comparison by Wilcoxon test showed evidence of significant difference from baseline at all evaluation points (p<0.001 in both cases), on PP and ITT populations.

- Subject acceptability of the drug, evaluated with the MSQ, improved through the study since in the ITT population, subject satisfaction level improved at least one grade, with respect to visit 4, for 47.0% of subjects at visit 5, while 62.5% of subjects improved their satisfaction level on visit 7-LOCF (63% on visit 7 evaluation). Similarly, on the PP population, 52.0% of subjects improved their satisfaction level with respect to visit 4, while, on visit 7-LOCF 63.3% did so (63.9% on visit 7) (Tables 48 and 50).

- Moreover, shift from visit 4, of investigator satisfaction with the study drug improved on 38.8% of cases at visit 5, while this happened on 51.3% of cases at visit 7 (50.8% at visit 7-LOCF), in the ITT population. In the PP population, the shift of investigator satisfaction from visit 4, was identified as improvement on 42.9% of cases at visit 5 and 53.6% at visit 7 (53.1% visit 7-LOCF).

- **Attitude towards the study medication.** In regards to the patient attitude towards the study medication, this improved through the study since 47.5% of subjects of the ITT population answered "Much better or better" at visit 2 (baseline), while 86.8% of cases of this population, answered this way at visit 7. On the PP population, 50.5% scored as better or much better at visit 2, and 85.9% at visit 7 did so.

- **Time to readiness for discharge.** Mean time-to-readiness for discharge, on observed data, in the ITT hospitalized population was 40.9 ± 23.4 days (14-74 days). And in the PP hospitalized population was 43.0 ± 23.8 days (14-74 days). Kaplan Meier estimation was not applied due to small sample size of hospitalized patients.

- **Protocol-defined treatment failure.** Protocol-defined treatment failure occurred in 14 patients (9.7%) of ITT population at a mean time since the first dose of 54.0 ± 38.0 days (2-123 days). Reasons for treatment failure were: 6 substantial clinical deteriorations, 5 discontinuations of antipsychotic treatment due to inadequate efficacy, 4 suicidal behaviors, and, 3 discontinuations of antipsychotic treatment due to safety or tolerability (patients may have 2 different reasons).

- Protocol-defined treatment failure occurred in 4 patients (4.0%) of PP population at a mean time since the first dose of 75.0 ± 54.0 days (3-123 days). Reasons for treatment failure were: Two substantial clinical deteriorations and 2 suicidal behaviors.

SAFETY RESULTS:

There were 215 TEAEs in 92 patients (63.9%) (only those with a frequency >5.0%) displayed in the inferior table. Two of them (1.4%) were severe (psychotic disorder and weight decreased) and only 21 were considered by the investigator as very likely related to the drug under study [not showed in this table because their frequency was less than 5% (1.4%)]. One treatment was stopped due to a TEAE.

Further, there were 3 safety events (2.1%), two failures of expected pharmacologic effect and one not specified (0.7%).

Body system Preferred Term	N (%)
Gastrointestinal disorders	13 (9.0)
General disorders and administration site conditions	16 (11.1)
Procedural pain	12 (8.3)
Infections and infestations	8 (5.6)
Investigations	14 (9.7)
Weight increased	11 (7.6)
Metabolism and nutrition disorders	10 (6.9)
Nervous system disorders	64 (44.4)
Akathisia	16 (11.1)
Insomnia	13 (9.0)
Muscle rigidity	17 (11.8)
Somnolence	9 (6.3)
Tremor	8 (5.6)
Psychiatric disorders	22 (15.3)
Anxiety	8 (5.6)

STUDY LIMITATIONS:

Sample size was considered near to 150 patients; however, only 100 patients were available for PP population analysis. Forty-four patients (30.6%) of the ITT population were excluded of the PP population analysis by violations to inclusion/exclusion criteria, loss during follow-up and non-compliance with drug.

Due to small sample sizes of inpatients at the beginning of study and of treatment failure cases, Kaplan Meier estimations of time to discharge and time to treatment failure were not perform, in such cases listings of time by patients were provided. Although the SAP mentioned LOCF assessment to treatment

failure, it was not realized since the nature of the measure and the small sample size would give an irrelevant assessment.

Readiness to discharge questionnaire was not available to all inpatients and all visits were it should have been applied. In many cases, the formats were not sent to data management center.

InterSePT Scale for Suicidal Thinking-Plus questionnaire was not applied to all cases where the short version demanded it. The formats were not sent to data management center.

Due the open label methodology of this trial, it is difficult to conclude efficacy of the drug administered once monthly.

CONCLUSIONS:

More than 80% of patients with schizophrenia treated with paliperidone palmitate given once monthly during four months showed at least a 30% reduction of their symptomatology from baseline, evaluated with the PANSS score. This improvement in the symptomatology was accompanied of a better functional state measured by the PSP scale.

Additionally, patients had a statistically significant relief of their global severity of illness scored with the CGI-S.

Paliperidone palmitate was progressively accepted by patients whom expressed their satisfaction with the study drug in the MSQ. Investigators expressed increased satisfaction with the treatment through the same instrument throughout the study.

Subject's attitude regarding the study drug continuously improved over time considering better or much better in the 47.5% of cases at visit 2 and 86.8% at visit 7 on ITT population.

Regarding to readiness for hospital discharge, mean time was 40.9 ± 23.4 days in the ITT population similar to the 43.0 ± 23.8 days in the PP population.

There were 215 SSEs in 92 patients (63.9%). However, only two were severe (psychotic disorder and weight decreased) and only 21 were considered by the investigator as very likely related to the drug under study. Only one treatment was stopped due to a SSE. Most of AEs have been previously reported.

Paliperidone palmitate showed an excellent profile of efficacy/safety in patients with early diagnose of schizophrenia in an acute exacerbation of psychotic symptoms reducing the symptomatology, increasing their functionality and obtaining a good perception of the treatment.

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.