SYNOPSIS

Name of Sponsor/Company	Janssen EMEA*
Name of Finished Product	XEPLION® (also marketed as INVEGA® SUSTENNA® in some countries/regions)
Name of Active Ingredient(s)	R092670 (paliperidone palmitate)

* Janssen EMEA is an organization in Europe, the Middle East and Africa that operates through different legal entities in various countries. The legal entity acting as the sponsor for studies of Janssen EMEA may vary, such as, but not limited to Janssen Pharmaceutica NV or Janssen-Cilag International NV. 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: 13 July 2015
Prepared by: Janssen Pharmaceutica NV

Protocol No.: R092670SCH4017

Title of Study: HOSPItal Use of Paliperidone Palmitate - A Prospective Non-Interventional Study

Study Name: HOSPIPalm

NCT No.: NCT01926912

Clinical Registry No.: CR100862

Coordinating Investigator(s): This was an international, multicenter study, designed and conducted by the sponsor. No coordinating or overall principal investigator was assigned for this study.

Study Center(s): A total of 61 sites took part in 9 countries across the EMEA region: Belgium (3 sites), Bulgaria (7 sites), Denmark (2 sites), Germany (11 sites), Greece (5 sites), Israel (2 sites), Italy (14 sites), Kazakhstan (6 sites), Russia (11 sites).

Publication (Reference): None.

Study Period: 29 May 2013 to 27 August 2014

Phase of Development: Non-interventional

Objectives: The objectives of this study were:

- To explore the safety, tolerability, and appropriate use of the paliperidone palmitate (1-month formulation [PP1M]) initiation regimen in clinical practice in symptomatic adult patients with schizophrenia who were admitted to hospital due to an exacerbation of their disease.
- To describe treatment outcomes in hospital settings and patterns of use of PP1M in different countries in the EMEA region (Europe, the Middle East and Africa).

Methodology: This was a prospective, 6-week, multicenter, observational study. Eligible subjects were adult male or female patients with an established diagnosis of schizophrenia, who were admitted to hospital due to an exacerbation of their disease, and for whom PP1M was scheduled to be initiated within 3 weeks after admission to hospital. The decision to initiate treatment with PP1M must have been made prior to offering enrollment and in accordance with clinical practice.

Data were collected only in patients who, in the opinion of the participating physician, had the capacity to provide consent and provide their written consent for data collection (participation agreement/informed consent form [ICF]) before any study-related documentation. The participation of a patient in this study was to in no way impact upon the regular care of the patient or on any benefits to which they would otherwise have been entitled. All treatment decisions were made at the discretion

of the participating physician, per clinical practice. Only data available from clinical practice were collected. Diagnostic assessments and therapeutic regimens were not predefined, as all modalities of treatment (dosage etc.) remained the sole decision of the participating physician.

Patients' baseline data were collected at the time of initiation of treatment with PP1M (ie, the first injection), after provision of written consent signed by the subject and/or by his/her legal representative where applicable per local requirements. During the observation period, data available from clinical practice were collected in weekly intervals for up to 6 weeks after baseline. For each individual patient, data collection ended at Week 6 (Day 43 ±7 days) or at the time of premature discontinuation from the study.

Number of Subjects (planned and analyzed): A total of 367 patients were documented in the study and received at least 1 dose of paliperdione palmitate. Initially it was intended to document a total of 450 patients but enrollment was lower than expected. Nevertheless, a total of 367 patients was considered reasonable to allow for meaningful statistical analysis according to the objectives of this study.

Diagnosis and Main Criteria for Inclusion: Eligible patients were men or women aged ≥18 years with an established diagnosis of schizophrenia, who were admitted to hospital due to an exacerbation of their disease and who, in the opinion of the participating physician, may have benefited from treatment with PP1M, which was to be initiated within 3 weeks after admission to hospital. Patients must have had, in the opinion of the participating physician, the capacity to provide consent. Prior to any documentation in this study, all patients and/or their legal representative must have signed a participation agreement/ICF allowing source data verification in accordance with local requirements.

Patients meeting the following criteria were not eligible: known hypersensitivity to paliperidone or risperidone; previous treatment with PP1M; history of neuroleptic malignant syndrome; antipsychotic treatment of schizophrenia with clozapine or previous treatment with any long-acting injectable antipsychotic during the last 3 months; received an experimental drug or used an experimental medical device within 30 days before the planned start of treatment; and/or were involuntarily hospitalized at the beginning of data collection.

Test Product, Dose and Mode of Administration, Batch No.: This was a non-interventional observational study. Paliperidone palmitate (1-month formulation [PP1M]) was obtained from commercial sources and was not provided by the sponsor.

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

Duration of Treatment: There was no pre-specified treatment duration. The 6-week observational period started from the first PP1M injection (Day 1) and continued until Week 6 (Day 43 ±7 days) or premature discontinuation.

Criteria for Evaluation: Safety and tolerability assessments included monitoring of all adverse events and assessment of body weight and Extrapyramidal Symptom Rating Scale (ESRS) scores.

Treatment response was assessed using the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI)-Severity scale (CGI-S), CGI-Change scale (CGI-C), and the Personal and Social Performance (PSP) scale. Patient satisfaction with medication was assessed using the Medication Satisfaction Questionnaire (MSQ).

The BPRS, PSP, and ESRS scales were performed only if consistent with routine practice at the respective study site.

Statistical Methods:

Sample Size Considerations: The target of approximately 450 patients was defined to allow collection of data on a sample of symptomatic patients with schizophrenia who were admitted to hospital due to an exacerbation of their disease, and to allow for exploratory analyses of patient subgroups.

Enrollment of patients was lower than initially expected. Nevertheless, the final number of patients documented in this study (N=367) was considered reasonable to allow for a meaningful statistical analysis according to the objectives of the study.

Analysis Sets: All documented patients who provided their written consent for data collection and who received at least one dose of PP1M in this study (referred to as the 'documented population') were included in the statistical analyses. Analysis of treatment response was conducted using the efficacy analysis set, comprising all patients in the documented population who provided at least one postbaseline treatment response assessment. Safety analyses were conducted using the safety analysis set, defined as all patients in the documented population who provided any postbaseline safety information.

Subgroup Analysis: According to the design of this study, patients were eligible to participate if they were hospitalized due to an exacerbation of schizophrenia and if treatment with PP1M was initiated within the first 3 weeks after admission to the hospital. As symptom severity at baseline was not specified in the selection criteria, there was a large variation in symptom severity at baseline (with individual BPRS total scores ranging from 20 to 101). In order to explore potential differences in treatment response and/or the tolerability of PP1M in relation to baseline symptom severity, a subgroup analysis was performed in the subset of patients who fulfilled widely accepted criteria for acute symptom severity at baseline (patients with a BPRS total score ≥42 and CGI-S score ≥moderately ill). This subgroup was referred to as the "acute" subgroup.

All analyses described below were performed on the total study population as well as on the acute subgroup. Analyses of other subgroups may also be performed in the future, results of which will be reported separately.

Treatment Response: Observed values and changes from baseline for continuous/ordinal efficacy variables (eg, BPRS, CGI-S, PSP) were summarized descriptively at each time point and at endpoint (last observation carried forward [LOCF]). In addition, frequency distributions of the proportions of patients within CGI-S, CGI-C, and PSP categories, and the proportion of patients who showed an improvement in their 10-point PSP category score (ie, moved from one 10-point category at baseline to a higher 10-point category at endpoint) were presented. The proportion of patients that showed a ≥30% or ≥50% decrease (ie, improvement) in BPRS total score from baseline over time was summarized as frequency distribution.

Hospital Discharge: The time to discharge since admission and the time to discharge since first injection of PP1M were analyzed using Kaplan-Meier product-limit survival curve estimates.

Safety Analysis: Safety and tolerability analyses included descriptive summaries of treatment-emergent adverse events (TEAEs), changes in body weight/body mass index (BMI), and changes in ESRS total score and subscores from baseline.

RESULTS:

STUDY POPULATION:

Total Population: Of the 367 patients in the documented population, 65.9% were male. The mean (standard deviation [SD]) age was 39.8 (12.12) years and mean (SD) BMI was 26.0 (4.84) kg/m^2. Most patients (85.8%) had a diagnosis of paranoid subtype schizophrenia. The mean (SD) time from hospital admission to initiation of PP1M was 9.4 (7.74) days.

A total of 336 (91.6%) patients completed the 6-week observational period. The most frequent reasons for early discontinuation were loss to follow-up (2.7%), withdrawal of consent (1.6%), and withdrawal due to sponsor decision (selection criteria not met) (1.6%).

Most patients (96.5%) had received an oral antipsychotic within the 4 weeks prior to study entry and more than than half the patients (54.2%) were on antipsychotic polytherapy. Overall, 68.7% were on atypical antipsychotic medication and 59.1% were on conventional antipsychotic medication.

Concomitant medication was used in 87.2% of patients. The most common concomitant medications were trihexyphenidyl (used in 18.3% of patients), oral paliperidone extended-release (ER) (16.1%), oral risperidone (15.8%), biperiden (15.5%), and haloperidol (15.3%).

The recommended PP1M initiation regimen (150 mg eq. on Day 1 and 100 mg eq. on Day 8, both in the deltoid muscle) was used in 88.8% of patients. The mean (SD) duration of PP1M exposure during the observation period was 34.1 (9.13) days.

Acute subgroup: A total of 251 subjects in the documented population with a baseline BPRS total score ≥42 and a CGI-S score ≥moderately ill were included in the acute subgroup. Subject characteristics and treatment information for the acute subgroup were similar to those reported for the total population (see table below).

Overview of Subject and Treatment Information in the Total Population and the Acute Subgroup

	Total Population	Acute Subgroup
Documented Population	367	251
No (%) subjects who completed the observational period	336 (91.6%)	231 (92.0%)
Demographics		
Sex: % Male/Female	65.9/34.1	67.3/32.7
Mean (SD) age	39.8 (12.12)	40.0 (12.60)
Mean (SD) BMI	26.0 (4.84)	25.8 (4.55)
Disease Characteristics		
Schizophrenia subtype - Paranoid	315 (85.8%)	217 (86.5%)
Mean (SD) age at schizophrenia diagnosis	28.5 (9.83)	28.8 (10.23)
Mean (SD) years from diagnosis to start of the study	11.4 (10.52)	11.3 (10.54)
Mean (SD) number of previous hospitalizations	6.7 (7.12)	6.3 (5.94)
Current Hospitalization		
Main reason for initiating PP1M: partial or nonadherence	147 (40.1%)	105 (41.8%)
Main reason for initiating PP1M: efficacy	139 (37.9%)	90 (35.9%)
Mean (SD) time since hospital admission to first PP1M injection (days)	9.4 (7.74)	9.3 (7.13)
Exposure		
No. (%) patients who received recommended initation regimen	326 (88.8%)	224 (89.2%)
Mean (SD) number of exposed days	34.1 (9.13)	34.4 (8.46)

Note – Acute subgroup comprises all patients in the documented population with BPRS total score ≥42 and CGI-S score ≥"moderately ill" at baseline.
AP=antipsychotic; Conmed=concomitant medications; PP1M=paliperidone palmitate 1-month formulation

TREATMENT RESPONSE:

Total Population (efficacy analysis set; N=365): Mean (SD) BPRS total score decreased from 50.2 (13.64) at baseline to 30.8 (9.94) at endpoint (mean change: -19.3; p<0.0001), indicating an improvement in psychiatric symptom severity during the study. A statistically significant decrease in BPRS total score was observed on Day 8 (mean change -6.5; p<0.0001) and at every assessment thereafter. At endpoint, 86.0% of patients showed a clinically meaningful ≥30% reduction in BPRS total score from baseline and 69.6% showed a ≥50% reduction.

Mean (SD) CGI-S score showed a statistically significant decrease from baseline to endpoint (mean change: -1.4; p<0.0001), indicating an improvement in disease severity. A statistically significant (p<0.0001) decrease was observed on Day 8 and all assessments thereafter. The proportion of patients rated as "normal", "borderline mentally ill" or "mildly ill" according to the CGI-S increased from 7.0% at baseline to 58.0% at endpoint. At endpoint, 93.5% of patients were rated as improved (ie, "minimally improved", "much improved" or "very much improved") on the CGI-C scale.

The mean (SD) PSP total score showed a statistically significant increase (ie, improvement) from 49.4 (14.74) at baseline to 63.7 (14.93) at endpoint (mean change: 14.3; p<0.0001). At endpoint, 74.8% of patients showed an improvement in their 10-point PSP category score (ie, moved from one 10-point category at baseline to a higher 10-point category at endpoint).

At baseline, 23.7% of patients were satisfied (ie, "somewhat satisfied", "very satisfied", or "extremely satisfied") with their previous antipsychotic medication based on the MSQ. At endpoint, 80.9% of patients were satisfied with PP1M treatment.

Approximately 40% of patients had been discharged from hospital at study endpoint.

Acute subgroup (efficacy analysis set; N=250): Overall, the acute subgroup showed similar results to the total population in all assessments of treatment response (see table below):

Overview of Treatment Response in the Total Population and the Acute Subgroup

	Total Population	Acute Subgroup
Efficacy analysis set	365	250
BPRS Total score, N	329	237
Mean (SD) baseline score	50.2 (13.64)	56.1 (11.00)
Mean (SD) change from baseline to endpoint	-19.3 (12.63)***	-22.9 (12.37)***
No. (%) patients with ≥30% improvement from baseline to endpoint	283/329 (86.0%)	204/237 (86.1%)
No. (%) patients with ≥50% improvement from baseline to endpoint	229/329 (69.6%)	165/237 (69.6%)
CGI-S score[a], N	345	250
Mean (SD) baseline score	3.7 (0.85)	3.9 (0.74)
Mean (SD) change from baseline at endpoint	-1.4 (1.08)***	-1.5 (1.10)***
CGI-C score		
No. (%) patients improved[b] at endpoint	318/340 (93.5%)	227/244 (93.0%)
PSP Total score, N	294	209
Mean (SD) baseline score	49.4 (14.74)	45.8 (13.77)
Mean (SD) change from baseline at endpoint	14.3 (12.44)***	15.1 (13.22)***
MSQ		
No. (%) patients satisfied[c] with previous AP medication at baseline	79/334 (23.7%)	47/240 (19.6%)
No. (%) patients satisfied[c] with PP1M treatment at endpoint	271/335 (80.9%)	190/236 (80.5%)
Hospital Discharge		
No. (%) patients discharged at endpoint	151/365 (41.4%)	107/250 (42.8%)
Mean (SE) estimated time to discharge since admission	41.7 (1.08)	42.9 (1.23)
Mean (SE) estimated time to discharge since first injection of PP1M	30.1 (0.82)	30.9 (0.94)

Note – Acute subgroup comprises all patients in the documented population with BPRS total score ≥42 and CGI-S score ≥"moderately ill" at baseline.
***p<0.001 versus baseline (Wilcoxon Signed Rank test).
[a] CGI-S score: 0=normal, not at all ill; 1=borderline mentally ill; 2=mildly ill; 3=moderately ill; 4=markedly ill; 5=severely ill; 6=among the most extremely ill patients.
[b] "minimally improved", "much improved", or "very much improved".
[c] "somewhat satisfied", "very satisfied", or "extremely satisfied".
AP=antipsychotic; PP1M=paliperidone palmitate 1-month formulation.

SAFETY RESULTS:

Total population (safety analysis set; N=367): A total of 84 (22.9%) patients reported at least 1 TEAE during the 6-week observational period. TEAEs reported in ≥2% of patients were tremor (2.5%) and schizophrenia (2.2%). Most TEAEs were considered mild or moderate in severity. Ten (2.7%) patients reported a TEAE that was of severe intensity.

Thirteen (3.5%) patients reported at least 1 serious TEAE, including 2 patients who died following a serious TEAE of viral pneumonia and loss of consciousness, respectively. Both TEAEs with fatal outcome were considered unrelated to study drug by the investigator.

Four (1.1%) patients were withdrawn from study due to a TEAE (including 2 patients who died, and 2 patients with TEAEs of extrapyramidal disorder and akathisia, respectively).

Mean ESRS total score showed a statistically significant decrease from baseline to endpoint (mean change: -1.7; p<0.0001), indicating an improvement in EPS during the study.

Mean body weight showed a statistically significant increase from baseline to endpoint (mean change: 0.95 kg; p<0.0001), and a total of 34 (9.7%) patients experienced a ≥7% increase in body weight from baseline to endpoint.

Acute Subgroup (safety analysis set; N=251): Safety results in the acute subgroup were comparable to those reported in the total population (see table below).

Overview of Safety Results in the Total Population and the Acute Subgroup

	Total Population	Acute Subgroup
Safety analysis set	367	251
Adverse Events, N	367	251
No. (%) patients with one or more TEAE	84 (22.9%)	65 (25.9%)
No. (%) patients with one or more causally related TEAE	42 (11.4%)	33 (13.1%)
No. (%) patients with one or more serious TEAE	13 (3.5%)	10 (4.0%)
No. (%) patients with one or more TEAE leading to permanent stop	4 (1.1%)	2 (0.8%)
No. (%) patients with TEAE with fatal outcome	2 (0.5%)	1 (0.4%)
ESRS Total Score, N	291	208
Mean (SD) baseline score	3.7 (5.94)	4.4 (6.57)
Mean (SD) change from baseline at endpoint	-1.7 (4.78)***	-2.0 (5.24)***
Body Weight, N	349	238
Mean (SD) baseline	76.39 (15.50)	76.38 (15.10)
Mean (SD) change from baseline at endpoint	0.95 (3.06)***	0.98 (3.13)***
No. (%) patients with ≥7% increase from baseline to endpoint	34/349 (9.7%)	27/238 (11.3%)
BMI, N	349	238
Mean (SD) baseline	25.95 (4.83)	25.75 (4.56)
Mean (SD) change from baseline at endpoint	0.32 (1.03)***	0.34 (1.06)***

***p<0.001 versus baseline (Wilcoxon Signed Rank test).

STUDY LIMITATIONS: This was a single-arm, open-label, observational study designed to document the use of PP1M in a routine clinical setting. The study was not intended to compare treatment with PP1M to any other treatment. No notable study limitations were identified by the Sponsor. Patient enrollment was lower than expected, but the final number of enrolled patients was considered to be appropriate for analysis and the lower sample size was not considered to have had a significant impact on the conclusions of the study.

CONCLUSION(S): This was a non-interventional study designed specifically to document treatment outcomes in patients with schizophrenia who had recently been admitted to hospital due to an exacerbation of their disease in routine clinical practice and who initiated treatment with PP1M within the first 3 weeks of their hospital stay. The observation period of 6 weeks was chosen to likely cover the average length of hospital stay in different countries in the EMEA region. Study results showed the mean time from hospital admission to initiation of PP1M was short (9.4 days) and the initiation regimen was used according to the label in a high proportion of patients (88.8%).

Treatment with PP1M in this 6-week observational study was overall well tolerated and associated with an early, statistically significant and clinically meaningful improvement in psychiatric symptom severity and patient functioning in the studied population. Patient satisfaction with PP1M treatment at study endpoint was higher than rated for previous oral antipsychotic medications at baseline. No new safety signal was observed in this study population.

Overall, results of this study suggest that patients may benefit from an early initiation of PP1M during their hospital stay.

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