SYNOPSIS

Name of Sponsor/Company	Janssen EMEA*
Name of Finished Product	INVEGA® SUSTENNA®; XEPLION®
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 Janssen EMEA studies may vary, such as, but not limited to Janssen Pharmaceutica NV or Janssen-Cilag International. The term "sponsor" is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved

Date: 13 November 2013

Prepared by: Janssen EMEA

Protocol No.: R092670SCH3010

Title of Study: A 6-Month, Open-Label, Prospective, Multicenter, International, Exploratory Study of a Transition to Flexibly-Dosed Paliperidone Palmitate in Patients with Schizophrenia Previously Unsuccessfully Treated with Oral or Long-Acting Injectable Antipsychotics

Study Name: PALMFlexS

EudraCT Number: 2009-018022-30

NCT No.: NCT01281527

Clinical Registry No.: CR017215

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

Study Center(s): A total of 160 sites took part across the EMEA region: Austria (1 site), Belgium (9 sites), Croatia (2 sites), Denmark (1 site), Estonia (1 site), France (15 sites), Germany (20 sites), Greece (6 sites), Hungary (4 sites), Israel (3 sites), Italy (20 sites), Latvia (6 sites), Lithuania (3 sites), Netherlands (1 site), Portugal (7 sites), Spain (19 sites), Sweden (5 sites), Switzerland (2 sites), Turkey (11 sites), Ukraine (15 sites), United Kingdom (9 sites).

Publication (Reference): None.

Study Period: 02 November 2010 – 14 November 2012. Database lock was on 19 March 2013.

Phase of Development: Phase 3b.

Objectives: The primary objective was to explore the tolerability, safety, and treatment response (maintained/improved efficacy; based on the total Positive and Negative Syndrome Scale [PANSS] score) following a transition to flexibly-dosed once-monthly paliperidone palmitate (PP) in patients with schizophrenia previously unsuccessfully treated with oral or LAI antipsychotics. Acute and non-acute patients were eligible to enter the study.

Secondary objectives were to collect additional data to develop recommendations for use of, and transition to, PP from previous oral and long-acting injectable (LAI) antipsychotic medications through evaluation of efficacy, safety, and other clinically important endpoints (see **Criteria for Evaluation**).

Methodology: This was a non-randomized, single-arm, multicenter, open-label, 6-month, interventional study including approximately 1,000 patients with schizophrenia. The study consisted of a screening period, a 6-month study period, and an optional open-label extension phase.

Three groups of subjects were pre-specified:

- **Group A** included approximately 600 non-acute but symptomatic patients with schizophrenia who were transitioned to PP because of prior unsuccessful treatment with an oral antipsychotic in the 4 weeks prior to enrollment.
- **Group B** included approximately 200 non-acute but symptomatic patients with schizophrenia who were transitioned to PP because of prior unsuccessful treatment with a frequently-used LAI antipsychotic (ie, haloperidol decanoate, flupentixol decanoate, fluphenazine decanoate, zuclopenthixol decanoate, or risperidone LAI) in the 4 weeks prior to enrollment. The target was to recruit approximately 40 patients per prior LAI antipsychotic group.
- **Group C** included approximately 200 patients with acute symptoms of schizophrenia who were transitioned to PP because of unsuccessful treatment with an oral antipsychotic in the 4 weeks prior to enrollment.

Subjects in Group A and Group C were additionally stratified into 2 subgroups according to the time since diagnosis of schizophrenia (ie, >3 years or ≤3 years).

The start of the 6-month study period was defined as the day of the first PP injection (baseline, Day 1). Subjects who transitioned from oral antipsychotics were scheduled to receive their first injection of PP (150 milligrams equivalent [mg eq.]) on Day 1 and their second injection (100 mg eq.) 1 week later (Day 8), followed by monthly injections thereafter. A transition period of preferably a maximum of 4 weeks was allowed for tapering off the previous oral antipsychotic. Subjects who transitioned from another LAI were to receive their first PP injection in place of the next scheduled dose of their previous LAI, followed by monthly injections thereafter. Monthly PP maintenance doses could be adjusted flexibly within the range of 50 to 150 mg eq.

Subjects who successfully completed the 6-month study period and who wanted to continue treatment with PP could enter an optional extension phase. This report describes results of the 6-month study period only; results of the optional extension phase will be reported separately.

Number of Subjects (planned and analyzed): The planned total sample size was 1,000 (600 in Group A, 200 in Group B [40 subjects in each of the 5 LAI subgroups], and 200 in Group C). The actual analysis sets are described below:

Data Sets Analyzed: All Subjects Analysis Set

	Group A	Group B, Switched from one of the following LAIs:					Group C
	Total Non-acute (N=599)	Haloperidol Decanoate (N=53)	Flupentixol Decanoate (N=36)	Fluphenazine Decanoate (N=44)	Zuclopenthixol Decanoate (N=44)	Risperidone LAI (N=58)	Total Acute (N=214)
Enrolled	595(99.3)	53(100.0)	35(97.2)	44(100.0)	42(95.5)	57(98.3)	212(99.1)
ITT population[a]	593(99.0)	53(100.0)	35(97.2)	44(100.0)	42(95.5)	56(96.6)	212(99.1)
Safety population[b]	593(99.0)	53(100.0)	35(97.2)	44(100.0)	42(95.5)	56(96.6)	212(99.1)
Efficacy population[b]	589(98.3)	53(100.0)	34(94.4)	44(100.0)	41(93.2)	55(94.8)	207(96.7)

[a] ITT (intent-to-treat) population included all subjects who received at least 1 dose of study drug

[b] Safety and efficacy populations included all subjects in the ITT analysis set who had any post-baseline safety or efficacy data, respectively.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were men or women aged 18 years or older, with a current diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, who had been unsuccessfully treated with an oral or LAI antipsychotic, and who may have benefited from a switch to PP.

Subjects were either non-acute (Groups A and B) or acute (Group C) at baseline:

- Non-acute: Subjects received an oral antipsychotic (Group A) or LAI antipsychotic (Group B) given at an adequate dose and with a CGI-S change ≤1 in the past 4 weeks before enrollment, but current treatment was considered unsuccessful due to one or more of the following reasons:
  1) lack of efficacy (defined as subjects with a baseline PANSS total score ≥70 or ≥2 items scoring ≥4 in the PANSS positive or negative subscale or ≥3 items scoring ≥4 in the PANSS general psychopathology subscale, as judged by the investigator);
  2) lack of tolerability (defined as the presence of clinically relevant [ie, either clinically relevant according to the investigator and/or intolerable to the subject] side effects with the current antipsychotic medication);
  3) lack of compliance; or
  4) patient's wish.
- Acute: Subjects with acute symptoms of schizophrenia, previously treated with an oral antipsychotic, having a baseline PANSS total score ≥80 and a baseline Clinical Global Impression-Severity (CGI-S) score ≥4.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone palmitate aqueous suspension for once-monthly intramuscular injection was supplied by the sponsor in prefilled syringes of 50 mg eq., 75 mg eq., 100 mg eq., and 150 mg eq. dose strengths.

Strength	Batch numbers (Expiry dates)
50 mg eq.	9JTK01C (Sep-11), AJTK01K (Oct-12), BETK01H (May-13),CHTK00M (Jul-14)
75 mg eq.	9HTK01C (Jul-11); AJTK01J (Oct-12); BETK01G (May-13); BITK01Q (Sep-13); CHTK016 (Jul-14)
100 mg eq.	9HTK01B (Jul-11), AKTK00Q (Nov-12), BITK01P (Sep-13),BETK01F (May-13), CHTK014 (Jul-14)
150 mg eq.	9JTK01B (Sep-11), AJTK01L (Oct-12), BFTK011 (Jun-13), BITK018 (Sep-13), CHTK017 (Jul-14)

Paliperidone extended-release tablets for oral tolerability testing (in patients without prior exposure to paliperidone or risperidone) were provided by the sponsor in 3-mg tablet strengths.
Batch numbers (Expiry dates): 8ETK02V (May-11), 91TK01N (Sep-12), AKTK02B (Nov-13).

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

Duration of Treatment: This report describes results of the 6-month study period. The first injection of PP was given on Day 1 and the last injection was scheduled to be given on Day 151 (± 7 days) for Group B or on Day 158 (± 7 days) for Groups A and C.

Criteria for Evaluation: The following rating scales were used to assess efficacy: PANSS; CGI-S, Clinical Global Impression-Change Scale (CGI-C); and Personal and Social Performance Scale (PSP).

Tolerability and safety were monitored by evaluating adverse events, vital signs, physical examination, body weight/body mass index (BMI), and assessment of extrapyramidal symptoms (using the Extrapyramidal Symptom Rating Scale [ESRS]).

Other assessments included: the self-reported health status questionnaire [SF-36]; EuroQol 5-dimensional Questionnaire (EQ-5D); Subjective Well-Being under Neuroleptics Scale, Short form [SWN-S]); quality of sleep and daytime drowsiness (11-point categorical rating scales); patient satisfaction with medication (Treatment Satisfaction Questionnaire for Medication [TSQM]); Physician treatment satisfaction (7-point categorical scale); and Mini International Classification of Functionality, Disability and Health Rating for Activity and Participation Disorders in Psychological Illnesses [Mini-ICF-APP].

Exploratory assessments included: measures of alcohol and substance use (using the Clinician Rating [CR] Alcohol Use Scale [CRAUS] and CR Substance Use Scale [CRSUS]), Medical Resource Utilization

(assessed using the Healthcare resource use questionnaire [HRUQ]), "clear thinking" (using the Clear Thinking Scale [CTS]), and assessment of caregiver burden (using the Involvement Evaluation Questionnaire [IEQ]). CTS and IEQ were used in a limited number of countries only, depending on availability of the scale in the local language. Results of the CTS and results of the MRU assessments will be reported separately.

Statistical Methods: The primary endpoint was based on the change in PANSS total score from baseline to endpoint (last-observation carried forward [LOCF]).

- For Group A, the primary endpoint differed according to the reason for switching. In patients switched due to lack of efficacy, the primary endpoint was improved efficacy (ie, the proportion of patients with ≥20% improvement in PANSS total score at endpoint versus baseline). In patients switched due to other reasons, the primary endpoint was maintained efficacy, based on a non-inferior change according to the Schuirmann's test.
- For Group B, the objective was to descriptively explore tolerability, safety and treatment response of switching from each individual LAI antipsychotic to PP.
- For Group C, the primary objective was to investigate improved efficacy (ie, the proportion of patients with a ≥30% improvement in PANSS total score at endpoint versus baseline).

Actual values and changes from baseline (if appropriate) for continuous/ordinal variables (eg, PANSS, CGI-S, CGI-C, PSP, SF-36, EQ-5D, etc.), including subscales and summary scores, were summarized descriptively at each assessment time point and at the subject's last evaluation (LOCF endpoint). The change from baseline at each visit (observed values) and at LOCF endpoint was analyzed using the Wilcoxon signed-rank test. In addition, quantitative differences between subgroups at each visit (Groups A and C only) were analyzed using the Wilcoxon two-sample test.

Safety analyses included descriptive summaries of incidence of adverse events and changes in vital signs, body weight/BMI and ESRS scores from baseline.

RESULTS:

STUDY POPULATION:

Group A: 593 non-acute but symptomatic patients were included in the Group A intent-to-treat (ITT) analysis set; 63.1% were male, mean (SD) age was 38.4 (11.83) years, and 78.6% had a diagnosis of schizophrenia of paranoid subtype. The main reason for transition from prior oral antipsychotic treatment was patients wish (43.7%) followed by lack of efficacy (24.3%) and lack of compliance (23.3%). Overall, 74.5% of patients in the ITT analysis set completed the 6-month study. The most frequent reasons for early discontinuation from the study were withdrawal of consent (10.1%), adverse event (6.1%), lost to follow-up (3.2%), and lack of efficacy (2.5%). The recommended PP initiation regimen (150 mg eq. on Day 1 and 100 mg eq. on Day 8 ± 2 days, both in the deltoid muscle) was administered in 93.9% of subjects. The median mode dose was 100 mg eq.

Group B: 230 non-acute but symptomatic patients were included in the Group B ITT analysis set (35 to 56 per LAI switch group). Across the LAI switch groups, 57.1% to 69.8% of patients were male, mean age ranged from 39.9 to 44.4 years, and 71.4% to 81.8% of patients had a diagnosis of schizophrenia of paranoid subtype. The most common reason for switching was lack of efficacy in subjects switched from haloperidol decanoate (37.7%), flupentixol decanoate (54.3%), and zuclopenthixol LAI (38.1%), and patient's wish in subjects switched from fluphenazine decanoate (43.2%) and risperidone LAI (67.9%). Between 70.5% (fluphenazine decanoate) and 85.7% (flupentixol decanoate) of patients completed the study. The most common reasons for withdrawal were adverse event (4.8% to 10.7%) or withdrawal of consent (2.9% to 18.2%). The median mode PP dose was 100 mg eq. in all groups.

Group C: 212 acute patients were included in the Group C ITT analysis set: 59.0% were male, mean (SD) age was 36.4 (12.06) years, and 85.4% had a diagnosis of schizophrenia of paranoid subtype. The main reason for transition from prior oral antipsychotic treatment was lack of efficacy (45.8%) followed by lack of compliance (34.9%). Overall, 70.3% of patients completed the 6-month study. The most frequent reasons for early discontinuation were withdrawal of consent (9.4%), adverse event (9.0%), lost to follow-up (4.7%), and lack of efficacy (2.8%). The recommended initiation regimen of PP (150 mg eq. on Day 1 and 100 mg eq. on Day 8 ± 2 days, both in the deltoid muscle) was administered in 92.9% of subjects. The median mode dose was 100 mg eq.

EFFICACY RESULTS: Efficacy analyses were performed using the efficacy analysis set.

Group A: In non-acute patients who were switched due to lack of efficacy (N=143), 61.5% of patients met the primary endpoint of improved efficacy (ie, a ≥20% reduction in PANSS total score from baseline to endpoint [LOCF]). In patients switched due to other reasons (N=446), the primary endpoint was maintained efficacy; these patients actually showed a statistically significant improvement in PANSS total score from baseline to endpoint (LOCF) (mean [SD] change of -11.6 [16.16]; p<0.0001), with 64.8% achieving a ≥20% reduction in PANSS total score. Results of the Schuirmann's test rejected the null hypotheses of non-equivalence (p<0.0001).

Group B: The primary endpoint was to descriptively explore treatment response across the various LAI switch groups. As shown in the table below, all groups showed a statistically significant improvement in PANSS total score from baseline to endpoint (LOCF), with more than 50% of the patients in each group achieving a ≥20% reduction in PANSS total score.

Group C: In acute patients (N=212), 66.7% patients met the primary endpoint of improved efficacy (ie, a ≥30% reduction in PANSS total score from baseline to endpoint [LOCF]).

Improvements in PANSS total score were accompanied by improvements in secondary efficacy variables (PANSS subscales, PANSS Marder factors, CGI-S score, and PSP score; see key results below).

Key Efficacy Results: Changes from Baseline to Endpoint (LOCF) in PANSS, CGI-S, and PSP Score (Efficacy Analysis set)

	Group A	Group B, Switched from one of the following LAIs:					Group C
	Total Non-acute (N=589)	Haloperidol Decanoate (N=53)	Flupentixol Decanoate (N=34)	Fluphenazine Decanoate (N=44)	Zuclopenthixol Decanoate (N=41)	Risperidone LAI (N=55)	Total Acute (N=207)
PANSS total score							
Mean baseline	71.5	75.7	73.7	75.0	74.6	67.5	98.5
Mean change	-11.7**	-8.8**	-10.1*	-7.5*	-10.6*	-9.2*	-31.0**
PANSS Response[a] (%)	64.0%	54.7%	61.8%	59.1%	53.7%	61.1%	66.7%
CGI-S							
Mean baseline	3.9	4.2	3.9	4.0	4.1	3.7	5.0
Mean change	-0.6**	-0.4*	-0.4*	-0.4*	-0.5*	-0.4*	-1.5**
CGI-C[b]							
Mean endpoint	2.9	3.3	2.8	3.2	3.2	3.1	2.6
PSP Total score							
Mean baseline	58.1	48.7	59.6	53.5	52.9	60.1	43.9
Mean change	8.0**	5.2*	6.1*	6.0**	6.4*	5.2*	19.0**
% with PSP score ≥71							
Baseline	15.3%	3.8%	8.8%	6.8%	9.8%	32.7%	4.1%
Endpoint	40.8%	13.2%	35.3%	18.2%	22.0%	41.8%	37.1%

[a] PANSS response: ≥20% reduction in PANSS total score from baseline to endpoint (LOCF) in Non-acute patients (Group A and B) or ≥30% reduction in Acute patients (Group C).
[b] CGI-C score 2.0=much improved; 3.0=minimally improved.
*p<0.05; **p<0.0001 versus baseline (Wilcoxon Signed-Rank test).

OTHER EVALUATIONS: Other clinical parameters were analyzed using the efficacy analysis set.

In non-acute and acute patients switched from oral antipsychotics (**Group A** and **Group C**), symptom reduction was associated with statistically significant improvements in patient's abilities of participation and activation (Mini-ICF-APP) and patient-rated measures of health and well-being (EQ-5D, SWN-S, SF-36) (see table below). Statistically significant improvements were also observed in physician-rated and patient-rated (TSQM) treatment satisfaction scores, and sleep and daytime drowsiness scores.

In **Group B**, improvements in the above-mentioned parameters were observed in each of the LAI switch groups, but the observed changes did not always reach statistical significance.

Other Evaluations: Changes from Baseline to Endpoint (LOCF) in Functioning and Patient-Rated Measures of Health and Well-being (Efficacy Analysis set)

	Group A	Group B, Switched from one of the following LAIs:					Group C
	Total Non-acute (N=589)	Haloperidol Decanoate (N=53)	Flupentixol Decanoate (N=34)	Fluphenazine Decanoate (N=44)	Zuclopenthixol Decanoate (N=41)	Risperidone LAI (N=55)	Total Acute (N=207)
SWN-S Total Score							
Mean baseline	80.1	83.7	83.5	81.0	83.0	80.8	73.8
Mean change	5.4**	3.2*	8.3*	2.9	4.3*	3.6	9.7**
SF-36 (PCS/MCS)							
Mean baseline	48.5/35.3	49.4/38.1	49.3/37.8	46.9/36.6	48.7/36.2	49.2/35.8	47.3/28.7
Mean change	1.4**/5.7**	1.4/4.4*	2.2/6.8*	2.6*/2.9	-0.0/8.7**	0.1/5.4*	1.9*/11.0**
EQ-5D VAS							
Mean baseline	60.38	60.37	61.32	61.53	64.21	56.26	55.30
Mean change	8.30**	8.10	15.32**	4.95	7.30*	9.31*	12.15**
Mini-ICF-APP Total score							
Mean baseline	19.8	23.0	20.5	21.7	21.1	18.4	26.5
Mean change	-4.0**	-3.3*	-4.6*	-1.7*	-2.5	-2.6*	-8.0**

*p<0.05; **p<0.0001 versus baseline (Wilcoxon Signed-Rank test).
MCS=mental component summary; PCS=physical component summary

EXPLORATORY EVALUATIONS: Exploratory parameters (CRAUS, CRSUS and IEQ) were analyzed using the efficacy analysis set, unless specified otherwise (results of the CTS and results of the MRU assessments will be reported separately).

In all groups, median CRAUS and CRSUS scores were 1.0 (abstinent) at baseline and endpoint (LOCF), indicating minimal alcohol/substance use in this group of subjects.

The IEQ total score showed a statistically significant improvement from baseline to endpoint (LOCF) in Group A and Group C, but not in any of the LAI switch groups in Group B.

SAFETY RESULTS: All safety analyses were performed using the safety analysis set. Treatment-emergent adverse events (TEAEs) and serious TEAEs were also analyzed in 8 additional patients who were incorrectly enrolled and received PP during the study, but who were not allocated to any of Groups A, B or C.

Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

	Group A	Group B, Switched from one of the following LAIs:					Group C	Other[a]
Proportion of subjects with:	Total Non-acute (N=593)	Haloperidol Decanoate (N=53)	Flupentixol Decanoate (N=35)	Fluphenazine Decanoate (N=44)	Zuclo Decanoate (N=42)	Ris LAI (N=56)	Total Acute (N=212)	(N=8)
≥1 TEAE	354(59.7)	27(50.9)	14(40.0)	18(40.9)	23(54.8)	35(62.5)	135(63.7)	2 (25)
≥1 Related TEAE	228(38.4)	18(34.0)	7(20.0)	10(22.7)	15(35.7)	24(42.9)	94(44.3)	0
≥1 Severe TEAE	57 (9.6)	6 (11.3)	4 (11.4)	5 (11.4)	4 (9.5)	2 (3.6)	(14.6)	1 (12.5)
≥1 Serious TEAE	90(15.2)	12(22.6)	5(14.3)	4(9.1)	5(11.9)	8(14.3)	25(11.8)	2 (25)
≥1 TEAE leading to permanent stop	42(7.1)	5(9.4)	3(8.6)	4(9.1)	2(4.8)	6(10.7)	21(9.9)	0

[a] Including 8 treated patients who were not assigned to Groups A, B or C.
Ris = risperidone; Zuclo=zuclopenthixol

The most common TEAEs in Group A were injection site pain (12.3%), insomnia (8.6%), anxiety (6.7%), psychotic disorder (6.1%), and headache (5.6%).

The most common TEAEs in Group B differed across the various LAI switch groups; TEAEs reported at least once in all groups included insomnia (1.8% to 11.4%), psychotic disorder (5.7% to 10.7%), and injection site pain (2.9% to 9.1%).

The most common TEAEs in Group C were injection site pain (13.7%), insomnia (10.8%), psychotic disorder (10.4%), anxiety (6.1%), and headache (6.1%).

Four (n=4) subjects died during the study; 3 subjects died due to completed suicide and 1 died due to acute myocardial infarction. One additional patient died >70 days after the date of the last exposure to study medication (cause of death - lung adenocarcinoma). None of the deaths was considered related to study drug by the investigator.

The most common serious TEAEs (reported in ≥1% of subjects in the overall pooled safety analysis set) were psychotic disorder (4.4%), schizophrenia (2.1%), and anxiety (1.2%).

Potentially prolactin-related TEAEs were reported in 18 (3.0%) subjects in Group A, in 1 to 2 subjects per LAI switch group in Group B, and in 12 (5.7%) subjects in Group C.

There were statistically significant reductions from baseline to endpoint (LOCF) in the ESRS total score in Group A, Group C, and in all LAI switch groups in Group B, indicating a reduction in extrapyramidal symptoms.

No clinically relevant changes in vital sign parameters (systolic blood pressure, diastolic blood pressure, or pulse rate) were observed.

The mean change in body weight from baseline to endpoint (LOCF) was +1.2 kg in Group A (mean baseline: 81.7 kg), +2.6 kg in Group C (mean baseline: 78.4 kg), and ranged from -3.3 to +1.8 kg in Group B (mean baseline: 79.2 to 89.5 kg).

STUDY LIMITATIONS: Study limitations were the open-label and single-arm design.

CONCLUSION(S): Treatment with flexible maintenance doses of PP (50 to 150 mg eq. once monthly) was associated with improved clinical outcomes in psychotic symptoms, patient functioning, patient-rated health and well-being, treatment satisfaction, and sleep quality and daytime drowsiness in patients with schizophrenia previously unsuccessfully treated with oral or LAI antipsychotics, including both acutely ill and non-acute but symptomatic patients.

Paliperidone palmitate was generally safe and well tolerated. Results were consistent with the known safety profile of PP and no new safety signals were observed.

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