SYNOPSIS

Name of Sponsor/Company	Janssen Korea Ltd.
Investigational Product	Invega Sustenna® Inj.
Active Ingredient	R092670 (Paliperidone palmitate)

Status: Approved

Date: 14 April 2014

Prepared by: Janssen Korea Ltd.

Protocol number: R092670SCH4010 (Local No.: PALM-KOR-4001)

Study title: An open-label, comparative study of immediate or delayed switch to paliperidone palmitate in patients unsatisfied with current oral atypical antipsychotics to evaluate the evolution of medication satisfaction and adherence

Name of the study: SATISFACTION study

NCT number: NCT01682161

Clinical trial registry number: CR100740

Coordinating investigator: Kwon, Junsu, MD. Ph.D.- Seoul National University Hospital, 28 Yeongeon-dong, Jongno-gu, Seoul, Republic of Korea

Study centers: Gachon University Gil Medical Center, The Catholic University of Korea Bucheon St. Mary's Hospital, Korea University Guro Hospital, Korea University Anam Hospital, Korea University Ansan Hospital, Dankook University Hospital, Daegu Catholic University Medical Center, Seoul National University Bundang Hospital, Seoul National University Hospital, SMG-SNU Boramae Medical Center, Yeouido St. Mary's Hospital, Youngnam University Medical Center, Inje University Paik Hospital, Ilsan Paik Hospital, Chungbuk National University Hospital and The Catholic University of Korea Uijeongbu St. Mary's Hospital

Publication (reference): This study has not been published yet.

Study period: From January 12, 2012 to September 17, 2013

Phase of development: Phase 4

Objectives:

Primary objective

The primary objective of this study was to evaluate the patient satisfaction in immediate or delayed switch to paliperidone palmitate, as measured by the Medication Satisfaction Questionnaire (MSQ) at the final assessment compared to the baseline, in patients unsatisfied with current oral atypical antipsychotics.

Secondary objectives

The secondary objectives of this study were to evaluate the following variables as clinical responses after switching to paliperidone palmitate:

1) Proportion of unsatisfied group (score 1 to 4) and satisfied group (score 5 to 7), as determined by the MSQ
2) Changes in total score / subscales / symptom factors of Positive And Negative Syndrome Scale (PANSS)
3) Change in the score of overall Clinical Global Impression - Severity (CGI-S)
4) Change in the score of Personal and Social Performance (PSP) and the proportions of mild difficulties (71-100), varying degrees of disability (31-70) and poor functioning (1-30)
5) Change in the score of Treatment Satisfaction Questionnaire for Medication
6) Proportion of treatment discontinuation
7) Overall safety and tolerability assessments, including the following items;
    - Vital signs (blood pressure, pulse rate) and weight
    - Physical examinations
    - Laboratory tests
    - Electrocardiogram
    - Adverse events (AEs)

Methodology: This open-label, comparative, multicenter study was composed of maximum 14 days of Screening Phase, 21-week open-label Treatment Phase and study completion/premature discontinuation visit. At baseline assessment, subjects were randomized to either immediate switch group or delayed switch group in 1:1 ratio and started taking peliperidone palmitate from baseline assessment (immediate switch group) or from Visit 5 (delayed switch group).

Number of subjects (planned and analyzed): A total of 158 subjects, 79 in each group, was planned to be enrolled in the study. Numbers of planned, enrolled and analyzed subjects are presented in the table below.

Analyzed data sets: all subject analysis sets

	Immediate switch (N=) n (%)	Delayed switch (N=) n (%)	Total (N=) n (%)
Planned	79 (100)	79 (100)	158 (100)
Enrolled			170 (107.6)
Randomized	78 (98.7)	76 (96.2)	154 (97.5)
Safety Analysis Set	76(96.2)	65(82.3)	141(89.2)
Full Analysis Set	67 (84.8)	67 (84.8)	134 (84.8)
Per-Protocol Analysis Set	76 (96.2)	42 (53.2)	85 (53.8)

Note: Full Analysis Set included subjects who received the study drug and comparator (oral atypical antipsychotics) at least once, met the inclusion/exclusion criteria, and underwent MSQ assessment at least once in addition to the baseline assessment.

Note: Safety Analysis Set included all subjects who received the study drug at least once.

Diagnosis and main criteria for inclusion:

Inclusion criteria

- Male or female 20 to 65 years of age, inclusive
- Those who met diagnostic criteria for schizophrenia according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders Version IV)
- Those who were taking an identical oral atypical drug for schizophrenia for the previous 4 weeks prior to screening
- Those unsatisfied with current oral atypical antipsychotics with MSQ score ≤4 but may benefit from switching the drug, in terms of symptom improvement or tolerability, according to the investigator's judgment
- Those who understand the purpose and procedures required for the study, and signed an informed consent form indicating their willingness to participate in the study (by the subject or by the subject and by a legally acceptable representative)

Exclusion criteria

- Known or suspected allergy, hypersensitivity reaction (anaphylactic-like reaction) or intolerance to risperidone, paliperidone or any of their excipients (see IB)
- Risk of suicide
- Clozapine use within the 60 days prior to screening
- Use of long-acting injection, including paliperidone palmitate and risperidone, at least once within the 90 days prior to screening
- Pregnant or breast-feeding women
- Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator

Study drug, dosage and administration, and batch number:

Product Name	Lot Numbers	Reference No. (SAP Batch No.)	Expire Date (Y-M-D)
Invega Sustenna Inj. 39mg (25mg)	BABK000	P4001-01	2012-12-31
	BEBK000	P4001-02	2013-08-31
Invega Sustenna Inj. 78mg (50mg)	BABK000	P4001-01	2012-12-31
	BABK000	P4001-01	2012-12-31
Invega Sustenna Inj. 117mg (75mg)	BABK000	P4001-01	2013-02-28
	BABK001	P4001-02	2013-05-31
	BABK001	P4001-02	2013-05-31
Invega Sustenna Inj. 156mg (100mg)	BABK001	P4001-01	2013-03-31
	BABK001	P4001-01	2013-03-31
Invega Sustenna Inj. 234mg (150mg)	BABK000	P4001-01	2013-02-28

	BABK002	P4001-02	2013-05-31
	BABK002	P4001-02	2013-05-31

Comparator, dosage and administration, and batch number: Comparator included all oral atypical antipsychotics that are currently available in Korea (aripiprazole, amisulpride, olanzapine, risperidone, quetiapine, ziprasidone, paliperidone, blonanserin and zotepine). Comparators were not provided by the sponsor, and the investigator determined the dose according to his/her discretion. Batch numbers were not identified.

Duration of treatment: Overall 21 weeks

Criteria for evaluation:

The primary efficacy endpoint was the change in general medication satisfaction, which was measured by mean MSQ score change from baseline to the final assessment.

The secondary efficacy endpoints included positive and negative syndrome and general severity change, personal and social performance, medication satisfaction change and proportion of treatment discontinuation.

Medication adherence and percentage of doses consumed were monitored in the delayed switch group for exploratory purposes.

Statistical methods:

Sample size determination

It was assumed that immediate or delayed switch to paliperidone palmitate will result in a mean 0.6 or greater change in MSQ score from baseline to the final assessment in schizophrenia patients currently unsatisfied with oral atypical antipsychotics. For 90% power at two-sided significance level of 95% and standard deviation of 1.8, 95 subjects were required. With 40% dropout assumption, a total of 158 subjects were required, 79 subjects each in immediate and delayed switch groups. PASS program was used for sample size estimation.

Results:

Study population

A total of 170 subjects were enrolled, and 154 of them were randomized after screening. Full Analysis Set (FAS) included 134 subjects; 89 (66.4%) of them completed the study and 45 (33.6%) were prematurely withdrawn from the study. Reasons of withdrawal were mostly ‘withdrawal of consent’ in 22 (16.4%) subjects, followed by ‘symptom aggravation’ in 10 (7.5%), ‘AE’ in 7 (5.2%), ‘protocol violation’ in 3 (2.2%), ‘lost to follow-up’ in 2 (1.5%) and ‘others’ in 1. Among 67 subjects in the immediate switch group, 44 (65.7%) of them completed the study and 23 (34.3%) were prematurely withdrawn from the study. Among 67 subjects in the delayed switch group, 45 (67.2%) of them completed the study and 22 (32.8%) were prematurely withdrawn from the study. The most common reason of withdrawal was ‘withdrawal of consent’ in both group (10[14.9%] and 12[17.4%], respectively).

The subjects were male and female schizophrenia patients aged 20 to 65, who were unsatisfied with current oral atypical antipsychotics. Their MSQ score was 4 or less and the investigators assumed that they might benefit from switching the drug in terms of symptom improvement and tolerability.

A total of 141 subjects received the study drug at least once, 76 of them in the immediate switch group and 65 in the delayed switch group.

Efficacy results

Among 134 subjects in the FAS, the primary efficacy endpoint, change in MSQ score from baseline to the final assessment, was 0.88 (±1.33) and 95% confidence interval was from 0.65 to 1.11, indicating statistical significance. The difference satisfied the hypothesis of mean 0.6 difference.

Safety results

Subjects with AE/response

	[Immediate group] (N= 76) n (%)	[Delayed group] (N= 65) n (%)
At least one AE	55 (72.4)	37 (56.9)
At least one serious AE	3 (3.9)	2 (3.1)
Death	0 (0.0)	0 (0.0)
Treatment discontinuation due to an AE	6 (7.9)	1 (1.5)

AEs that occurred in minimum 5% of the subjects

Body system Preferred term	[Immediate group] (N=76) n (%)	[Delayed group] (N=65) n (%)
Nervous system disorders		
Akathisia	9 (11.8)	5 (7.7)
Sedation	5 (6.6)	0 (0.0)
Headache	4 (5.3)	5 (7.7)
Psychiatric disorders		
Insomnia	8 (10.5)	6 (9.2)
Anxiety	7 (9.2)	0 (0.0)
Schizophrenia *	x (x)	5 (7.7)
General disorders and administration site conditions		
Injection site pain	8 (10.5)	6 (9.2)
Fatigue	4 (5.3)	0 (0.0)

* Schizophrenia symptom aggravation

AEs occurred in 92 (65.2%) out of 141 subjects (n=207). The most common AE in the immediate group was akathisia (9 subjects [11.8%], n=11), followed by insomnia and injection site pain (8 subjects (10.5%) each; n=10 and n=8, respectively), anxiety (7 subjects (9.2%), n=7), sedation (5 subjects (6.6%), n=5), and headache and fatigue (4 subjects (5.3%) each; n=5 and n=6, respectively). In the delayed group, insomnia and injection site pain each occurred in 6 subjects (9.2%, n=6), and schizophrenia (schizophrenia symptom aggravation), headache and akathisia each occurred in 5 subjects (7.7%; n=5, n=6 and n=5, respectively).

Serious AEs occurred in 3 subjects (3.9%, n=3) in the immediate group and in 2 subjects (3.1%, n=2) in the delayed group. One case of akathisia was a serious AE that was related to the study drug and was relieved after study drug discontinuation. Death was not occurred.

Study limitation

There was no noticeable limitation that was confirmed by the sponsor.

Conclusions

Paliperidone palmitate improved medication satisfaction among schizophrenia patients unsatisfied with current oral atypical antipsychotics. Immediate switch to paliperidone palmitate could improve medication satisfaction more rapidly than delayed switch. Paliperidone palmitate was generally safe.

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