Name of Sponsor/Company: Janssen-Cilag Ltd.
Name of Finished Product: Invega™
Name of Active Ingredient: Paliperidone ER

Title of Study: An Open-label, PRospective Study to Evaluate Social Function and Overall Improvement of Paliperidone ER Treatment in Thai Schizophrenia Subject (PRESENT)	
CTMS No.: R076477SCH4037 Clinicaltrial.gov No, if applicable:	
Publication (Reference): None	
Study Period (years): Date of first enrollment: 17-Aug-09 Date of last completed: 27-Aug-10	**Phase of Development:** Phase 4
Objectives: 1. To collect the safety data of Paliperidone ER based on the incidence of adverse events (AEs). 2. To evaluate the efficacy of treatment of paliperidone ER indicated by clinical global impression scale (CGI-S) ratings and Personal and Social Performance (PSP) scale.	
Methodology: The study utilized an open-label design to evaluate the safety and efficacy of paliperidone ER among subjects with schizophrenia. Study duration was ten weeks and subjects could either be inpatient or outpatient. The recommended paliperidone ER starting and maintenance dose was 6 mg/day in most subjects. Some subjects may benefit from higher or lower doses. Therefore, throughout the study flexible dosing in a range of 3 to 12 mg/day were used.	

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Number of subjects (planned and analyzed):

Sample size calculation:

The sample size for detecting the incidence of adverse events from Paliperidone (Invega®) at 10% with significantly clinical improvement of the schizophrenia subjects depend on the hypothesized acceptable value and the acceptable deviation. The clinical improvement will be reveal with the 10-point increase of PSP score. With the 90% of statistical power and type I error (2-sided) 0.025, the 35-subjects are required to prove the hypothesis.

From initial 35 subject planned, there were 40 subjects enrolled in this study. Efficacy analysis was performed in 37 intent-to-treat populations. All 40 enrolled subjects were included in safety analysis.

Table 1. Number of subjects

	Number of subject n (%)
Planned	35
Enrolled	40 (100)
Completed	32 (80)
Intent-to-treat population[a]	37 (92.5)
Safety population[b]	40 (100)

[a] Intent-to-treat population (ITT) included enrolled subjects who took at least one dose of study medication and had at least one post baseline efficacy evaluation. In addition, ITT population did not include subjects who were early terminated due to change diagnosis and withdrawn consent.

[b] Safety population included enrolled subjects who took at least one dose of study medication.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Meet the DSM-IV criteria for schizophrenia;
2. Male or female, aged 18 years;
3. The subjects who unsatisfied with the previous treatment;
4. Have previously or currently on oral atypical antipsychotics

Exclusion criteria:

1. Serious unstable medical condition, including recent and present clinically relevant laboratory abnormalities;
2. History or current symptoms of tardive dyskinesia;
3. History of neuroleptic malignant syndrome;
4. Pregnant or breast-feeding female;
5. Female subject of childbearing potential without adequate contraception. Adequate contraception includes: abstinence, oral contraceptives, intrauterine devices, barrier method (diaphragm or condom) plus spermicide; Norplant TM or Depot Provera TM.
6. Participation in an investigational drug trial within 30 days prior to selection;
7. Previously or currently expose to Paliperidone ER
8. Known hypersensitivity to paliperidone ER or risperidone

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Test product, dose and mode of administration, batch number:
The recommended paliperidone ER starting and maintenance dose was 6 mg/day for most subjects. Flexible dosing in a range of 3 to 12 mg/day was prescribed depending on the investigator consideration.

Paliperidone 3-mg, 6-mg and 9-mg oral tablets were used. Subjects who require a daily dose of 12 mg paliperidone were prescribed two 6-mg tablets.

Duration of treatment: 10 weeks period

Reference therapy, dose and mode of administration, batch number: N/A

Criteria for Evaluation:

At first visit (screening/start of treatment), the subject's demographic data, medical history, previous and current therapy, weight, and overall eligibility of the subjects who participated in the trial were recorded. All time point analyses employed a last-observation carried forward for those subjects with missing data.

Efficacy:
Throughout study, subjects were evaluated efficacy using clinician rating and self rating scales.

Clinician rating scales included Clinical and Global Impressions-Severity (CGI-S) scale and Personal and Social Performance Scale (PSP). The CGI-S rating scale is used to evaluate severity of a subject's psychotic condition on a 7-point scale ranging from 1 (not ill) to 7 (extremely severe). CGI-S permits a global evaluation of the subject's condition at a given time. (Guy, 1976). The PSP scale is a clinician-reported measure of severity of personal and social dysfunction. PSP scale overall rating score ranging from 1-100, where higher score represent better personal and social functioning. (Morosini et al.,2000)

Subjects were rated for overall severity of illness at the baseline (visit 1) and 10-week (visit 4/ end of study) using Clinical and Global Impressions-Severity (CGI-S) scale. Subjects were also interviewed at the baseline (visit 1), end of 2-week (visit 2), 6-week (visit 3) and 10-week (visit 4/ end of study) using the 4-item PSP scale to assess personal and social functioning.

Self rating scale included subject satisfaction, quality of sleep and daytime drowsiness evaluation. Subjects were asked to rate their satisfaction with the antipsychotic treatment that they currently taking with 5-scale questionnaire at baseline (visit 1) and end of study (visit4). Subjects were also asked to rate their quality of sleep and daytime drowsiness at baseline (visit 1), end of 2-week (visit 2), 6-week (visit 3) and 10-week (visit 4/ end of study) using visual analog scale.

Efficacy measurements were analyzed in the intent-to-treat population which is defined as enrolled subjects who took at least one dose of study medication and had at least one post baseline efficacy evaluation. In addition, ITT population did not include subjects who were early terminated due to change diagnosis and withdrawn consent.

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Safety:

Safety assessment included adverse event evaluated at every schedule visits and at anytime during study period. Vital sign and physical examination were also performed to ensure safety of subjects.

The primary safety populations comprised all enrolled subjects who took at least one dose of study medication.

Statistical methods:

Analysis was done on intent-to-treat principle. All statistical tests were performed with an alpha level of 0.05. PASW® statistics software version 18.0 was used in the statistical analysis.

Descriptive analysis of the demographic variables and other baseline line variables were conducted using measures of central tendency and variation for quantitative variables and frequency distributions for categorical variables.

Assessment of safety included computation of the incidence of AE and presentation in a frequency distribution table.

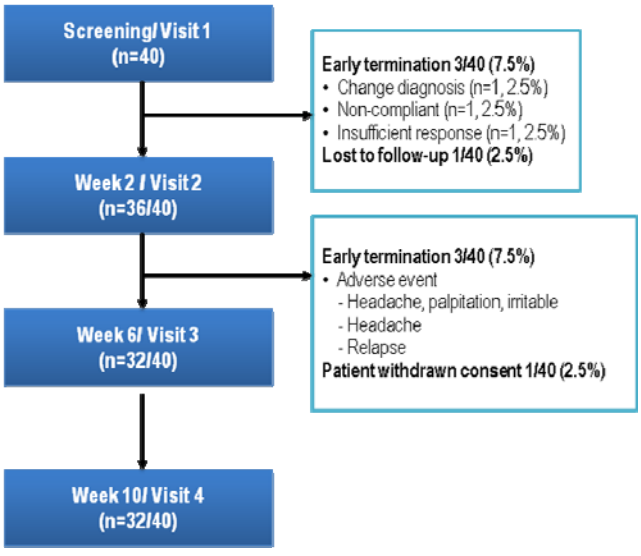
Paired t-test was performed on PSP scale to determine if there is a significant difference from baseline. Friedman test were performed on CGI-S to determine if there is a change in trend of the indicator from baseline.

SUMMARY – CONCLUSION

DEMOGRAPHIC RESULTS:

Study populations:

FIGURE 1. Subject disposition of An Open-label, Prospective Study to Evaluate Social Function and Overall Improvement of Paliperidone ER Treatment in Thai Schizophrenia Subject (PRESENT)



The total 40 subjects were enrolled and performed demographic evaluation at screening. 80% of enrolled subjects (n=32) completed the 10-week study (See Figure 1.). Reasons for early termination were change diagnosis (2.5%), non-compliant (2.5%), insufficient response (2.5%), lost to follow-up (2.5%), adverse event (7.5%) and subject withdrawn consent (2.5%).

Demographic and characteristic:

TABLE 2. Baseline demographic and clinical characteristic of intent-to-treat population (N=37)

	N	%
Sex		
Male	14	37.80
Female	23	62.20
Previous medications		
One oral typical AP	6	16.20
One oral atypical AP	16	43.20
Two oral typical APs	5	13.50
Two oral atypical APs	1	2.70
Oral typical AP+ oral atpical AP	5	13.50
One typical AP long acting injection	3	8.10
Oral typical AP + typical AP long acting injection	1	2.70
	Mean	**SD**
Age (years)	41.16	12.482
Weight (kg)	60.27	13.088
Height (cm)	1.59	0.087
BMI (Kg/m2)	23.60	3.863
CGI-S	3.57	1.168
PSP total score	57.03	18.008
Visual analog scale of quality of sleep	6.66	3.056
Visual analog scale of daytime drowsiness	3.219	2.420

A total 37 subjects were included in intent-to-treat (ITT) population (male=35.90%, female=64.10%). Mean $\pm$ SD age of subjects were 41.16 $\pm$ 12.482.

Common oral antipsychotic regimens before switching to paliperidone ER were one atypical antipsychotic (43.60%), one typical antipsychotic (16.20%), two atypical antipsychotics (13.50%) and typical combined with atypical antipsychotics (13.50%) respectively.

Baseline severity of subjects were classified as “mild” or “moderate ill” indicated by mean $\pm$ SD CGI-S score 3.75 $\pm$1.168. The mean $\pm$SD PSP total score, 57.03 $\pm$18.008 reflected progressive degrees of disability. (Morosini et al, 2000) The mean $\pm$ SD quality of sleep and daytime drowsiness rated by subjects were 6.66 $\pm$ 3.056 and 3.219 $\pm$ 2.420 respectively. (See Table 2.)

EFFICACY RESULTS:

Clinical and Global Impressions-Severity (CGI-S) scale:

TABLE 3. Distribution of CGI-S scale (N=37)

CGI-S distribution	Baseline (Week 0) n (%)	End point (Week 10) n (%)
Normal, not at all ill	2 (5.40)	5 (13.50)
Borderline mentally ill	3 (8.10)	13 (48.60)
Mildly ill	13 (35.10)	8 (21.60)
Moderately ill	12 (32.40)	9 (24.30)
Markedly ill	5 (13.50)	2 (5.40)
Severely ill	2 (5.40)	0 (0.00)
Among the most extreamly ill subject	0 (0.00)	0 (0.00)

At week 10 of paliperidone ER treatment, the CGI-S scale distributions showed reduction in severity from baseline. Majority of subjects were classified in 'Borderline mentally ill' (48.60%). Whereas, the most frequency of 'Mildly ill' at baseline (35.10%). There were fewer 'Mildly ill', 'Moderately ill' and 'Markedly ill' subjects at endpoint compared with baseline. (21.60% versus 35.10%, 24.30% versus 32.40% and 5.40% versus 13.50% respectively). In addition, there was no 'Severely ill' subject observed at endpoint (See Table 3).

Significant improvement from paliperidone ER efficacy were observed at endpoint by comparing mean CGI-S scale with baseline ($p<0.001$). The mean $\pm$ SD at end point was 2.73 ± 1.146. This result showed mean $\pm$ SD reduction for 0.84 ± 1.041 ($p<0.001$) from baseline (See Table 4).

TABLE 4. Change in CGI-S scale

Visit	Mean (SD)	Mean change from baseline	Mean rank		P value*
			Baseline	Endpoint	
Endpoint (Week 10)	2.73 (1.146)	0.84 (1.04)	1.78	1.22	0.000

Personal and Social Performance Scale (PSP):

TABLE 5. Change in PSP total score

Visit	Mean (SD)	Mean change from baseline	95% CI		P value*
			Lower	Upper	
Visit 2 (Week 2)	62.84 (13.843)	-5.81 (12.18)	-9.87	-1.75	0.006
Visit 3 (Week 6)	66.14 (14.759)	-9.11 (13.59)	-13.64	-4.58	0.000
Endpoint (Week 10)	69.03 (14.245)	-12.00 (16.43)	-17.48	-6.52	0.000

The significant improvements from paliperidone ER efficacy were observed at all time points by comparing PSP total score with baseline (See Table 5).

At week 2, the mean ± SD was 62.84 ± 13.843. This result showed mean ± SD change for -5.81 ± 12.18 (95% CI -9.87- -1.75) from baseline (**p<0.01).

At week 6, the mean ± SD was 66.14 ± 14.759. This result showed mean ± SD change for -9.11 ± 13.59 (95% CI -13.64- -4.58) from baseline (**p<0.01).

At week 10, the mean ± SD was 69.03 ± 14.245. This result showed mean ± SD change for -12.00 ± 16.43 (95% CI -17.48- -6.52) from baseline (***p<0.001).

An improvement of greater than or equal to 7-point interval on PSP scale is considered as clinical relevant response. In this study, there were 56.80% of subject showed clinical relevant improvement in social and functioning (See Table 6.)

TABLE 6. Clinical relevant improvement in PSP scale

Clinical relevant improvement	n	%
≥ 7-point improvement of PSP scale	21	56.80
< 7-point improvement of PSP scale	16	43.20
Total	37	100.00

Subject satisfaction:

TABLE 7. Distribution in subject satisfaction

Subject Satisfaction	Baseline (Week 0) n (%)	Endpoint (Week 10) n (%)
Very good	1 (2.70)	9 (24.30)
Good	14 (37.80)	19 (43.20)
Moderate	20 (54.10)	7 (18.90)
Poor	2 (5.40)	5 (13.50)
Very poor	0 (0.00)	0 (0.00)

Subject satisfaction toward the current medication changed significantly over the 10-week period (p=0.013). Subjects were more likely to satisfy with paliperidone ER at endpoint (67.60%) over baseline medications before switching to paliperidone ER (40.50%).

Quality of sleep:

TABLE 8. Change in quality of sleep

Visit	Mean (SD)	Mean change from baseline	SD	95% CI		P value*
				Lower	Upper	
Visit 2 (Week 2)	0.65 (0.308)	0.01	0.31	-0.90	0.11	0.818
Visit 3 (Week 6)	0.68 (0.344)	-0.01	0.39	-0.14	0.12	0.848
End point (Week 10)	0.72 (0.294)	-0.06	0.34	-0.17	0.06	0.303

All subjects were asked for quality of sleep evaluation with question, *How well have you slept in the past 7 nights?* The increasing number indicated improvement in quality.

The quality of sleep at endpoint was slightly increased from baseline. However, this improvement from paliperidone ER showed no statistical significant (p=0.30).

Daytime drowsiness:

TABLE 9. Change in daytime drowsiness

Visit	Mean (SD)	Mean change from baseline	SD	95% CI		P value*
				Lower	Upper	
Visit 2 (Week 2)	0.30 (0.303)	0.21	0.27	-0.68	0.11	0.636
Visit 3 (Week 6)	0.22 (0.264)	0.10	0.35	-0.02	0.21	0.090
End point (Week 10)	0.19 (0.259)	0.13	0.33	0.19	0.24	0.022

All subjects were asked for daytime drowsiness evaluation with question, *How often have you felt drowsy in the past 7 nights?* The decreasing number indicated lower in daytime drowsiness frequency.

The mean $\pm$ SD in daytime drowsiness frequency was gradually decreased from baseline at all time points. Significant decrease after using paliperidone ER was evident at week 10. ($p \leq 0.05$, 95% CI 0.19-0.24)

SAFETY RESULTS:

Safety analysis population included 40 subjects. 26 subjects (65%) with 53 adverse events were reported during study period. Most adverse events were mild to moderate in severity.

There were 3 subjects (7.5%) reported discontinuation due to adverse events. From total 53 adverse events, 96.23% of events were assessed non-serious in severity by investigators. 67.92% of all were assessed as related to the study medication. All related adverse events occurring in $\geq$ 5% of subjects are listed in Table 10.

Throughout study period, serious adverse events were reported in one subject (2.5%). The events were elevated mood and manic symptom. The investigator reported that the subject developed manic symptom and elevated in mood. At that time, the diagnosis was changed to schizoaffective disorder. This subject was hospitalized and treatment with paliperidone ER was withdrawn. Both manic symptom and elevated mood events were considered doubtfully related to study medication.

Extrapyramidal symptoms related adverse events were found in 4 subjects (10.0%). One subject was reported akathisia event. EPS were reported in other 3 subjects.

TABLE 10. Paliperidone ER treatment related adverse events occurring in ≥5% of subjects

Adverse event	n	%
Daytime drowsiness	6	15.00
EPS	3	7.50
Headache	3	7.50
Insomnia	3	7.50
Nausea	2	5.00
Vertigo	2	5.00
Total	19	47.50

After 10-week paliperidone ER treatment period, mean ± SD bodyweight of subjects increased from 60.27 ± 13.088 to 61.39 ± 13.065. Similarly to BMI, the mean ± SD BMI was increased from 23.60 ± 3.863 to 24.06 ± 3.937. A weight increase from baseline greater than or equal to 7% was observed in 8.10% of the subject and mean ± SD change in weight was 1.12 ± 2.190 (See table 11, table 12).

TABLE 11. Change in metabolic parameters (baseline to endpoint)

Metabolic parameters	Visit 1 (Baseline)	Visit4 (Week 10)	Change at end point	P value
Body weight (kg)	60.27 (13.088)	61.39 (13.065)	-1.12 (2.190)	0.004
BMI (kg/m2)	23.60 (3.863)	24.06 (3.937)	-0.46 (0.891)	0.003

TABLE 12. Frequency of subject gaining weight ≥ 7%

Weight gain	n	%
≥ 7%	3	8.10
< 7%	34	91.9
Total	37	100.00

CONCLUSION:

This study suggests that paliperidone ER is well tolerated in schizophrenia subject. Paliperidone ER showed significant improvement in schizophrenia symptom control and social functioning. No unexpected tolerability finding was observed. As such, paliperidone ER may be an effective option for schizophrenia treatment which provides social and functioning improvement among schizophrenic subjects.

Date of the report: 15-Jul-11

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