CLINICAL STUDY REPORT

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Name of Sponsor/Company	Janssen EMEA
Name of Finished Product	INVEGA®
Name of Active Ingredient(s)	Paliperidone ER

Protocol No.: R076477SCH4016

Title of Study: PILAR: Pharmacoepidemiologic International Longitudinal Antipsychotic Registry

Study Name: PILAR

EudraCT Number: Not Applicable

Coordinating/Principal Investigator(s): Not Applicable

Study Center(s): International multicenter study

Publication (Reference): None

Study Period: 26 May 2008 to 10 January 2011

Phase of Development: 4 (Non-interventional Study)

OBJECTIVES

The overall study objective was to document prescribing patterns in daily clinical practice and to assess long-term treatment outcomes related to initiation of treatment with oral antipsychotics in a naturalistic setting.

The primary objective of the study was to prospectively document treatment outcomes and healthcare utilization data that would enable a cost-effectiveness analysis of paliperidone extended release (ER) compared with other oral antipsychotic treatments. The effects over time on the following parameters were assessed:

- Time to treatment discontinuation
- Overall severity of symptoms
- Personal and social performance
- Health related quality of life and quality of sleep
- Healthcare utilization

An additional objective of the study was to retrospectively collect data that allowed the evaluation of treatment outcomes before and after treatment initiation with paliperidone ER or other oral antipsychotics.

METHODS

This was an international, non-interventional, observational study conducted in 12 countries in North America, Europe, and Asia on the use of paliperidone ER and other oral antipsychotic treatments conducted in patients with schizophrenia who were initiating any new oral antipsychotic treatment.

The study consisted of 2 parts: 1) a retrospective 1-year chart review and 2) a prospective 1-year period. Healthcare utilization data were collected during both periods. During the prospective period, clinician-administered evaluations, patient-reported health-related quality-of-life assessment, patient satisfaction assessment, and quality of sleep assessments (Visual Analogue Scale [VAS]) were documented. A patient

was considered to have completed the study if he/she completed all documentation at Month 12 of the prospective phase.

Number of Patients (Planned and Analyzed):

A total of approximately 787 patients (528 patients in the paliperidone ER arm and 259 in the 'other oral antipsychotic treatment' arm) across all countries or for an individual country was needed to detect, with an 80% power and a significant difference at alpha= 0.05, a between-group difference of 10% in treatment discontinuation.

Details regarding the patient enrollment and analysis set are provided in Table 1.

Table 1: Data Sets Analyzed (All Patients Analysis Set)

	Paliperidone ER (N=2204)	All other Antipsychotics] (N=825)	Total (N=3029)
Enrolled	2204	825	3029
Intent-to-treat population	2204	802	3006
Safety population	2204	825	3029

NOTE: Documentation was started for 3064 patients. 35 patients were excluded from analysis because they were not newly treated with paliperidone ER, oral conventional or oral atypical antipsychotics.
NOTE: Intent-to-treat population includes all patients documented in the study who are newly treated with paliperidone ER, oral conventional or oral atypical antipsychotics.
NOTE: Safety population includes all documented patients

Diagnosis and Main Criteria for Inclusion:

Patients of at least 18 years of age, inclusive; with a diagnosis of schizophrenia, and who had recently switched to or started on paliperidone ER or another oral antipsychotic treatment (either atypical or conventional) within 2 weeks of starting documentation in the study.

Period of Interest:

For each patient, there were 2 periods of interest:

- A retrospective period which captured data from 12 months prior to baseline and stopped the day before baseline (inclusive); and
- A prospective period, this covered the period from baseline up to 12 months after baseline.

Criteria for Evaluation:

Healthcare utilization data were to be collected during both the 1-year retrospective and prospective periods. The planned primary effectiveness endpoint was to compare initial treatment discontinuation rates over 12 months between the paliperidone ER group and the other oral antipsychotics group. Additional effectiveness endpoints were Clinical Global Impression-Severity (CGI-S), Clinical Global Impression-Schizophrenia (CGI-SCH), Personal and Social Performance (PSP), Physical Component Summary (PCS) and Mental Component Summary (MCS) scores of the SF-12v2 quality of life questionnaire, sleep VAS, clinical deterioration of psychiatric condition, and the patient's treatment satisfaction.

Adverse drug reactions (ADR) and serious adverse drug reactions (SADR) were documented for the retrospective period, and adverse events (AE) and serious adverse events (SAE) were reported during the prospective period, starting from the first intake of study medication. Safety evaluations in this observational study were considered as outcomes from the antipsychotic treatments received. Exploratory analyses to confirm the safety and tolerability signals observed in the pivotal paliperidone ER studies were conducted.

Statistical Methods:

A total of approximately 787 patients (528 patients in the paliperidone ER arm and 259 in the 'other oral antipsychotic treatment' arm) across all countries or for an individual country was needed to detect a between-group difference of 10% in treatment discontinuation, with an 80% power and a significant difference at alpha= 0.05.

Continuous variables were summarized using N, mean, standard deviation (SD), median, and range for all except the time-to-event variables. For categorical variables, the number and percentage of patients in each category was provided.

Repeated measures (assessments by time-interval) were analyzed as follows: (1) Observed cases; (2) Endpoint analysis, and (3) Mixed model.

All statistical tests were interpreted at the 5% significance level (2-tailed).

Primary effectiveness endpoint: The primary effectiveness endpoint was to compare the initial treatment discontinuation rate over 12 months between the paliperidone ER group and the other oral antipsychotics group. Kaplan-Meier plots were made and results were descriptively presented. A logrank test was performed to evaluate the null hypothesis. A Cox proportional hazard model with possible covariate adjustment was also performed to assess differences in the time to treatment discontinuation between the treatment groups.

Additional endpoint: Additional endpoints were CGI-S, CGI-SCH, PSP, PCS and MCS scores of the SF-12v2 quality of life questionnaire, Sleep VAS, clinical deterioration of psychiatric condition and the patient's treatment satisfaction. Treatment groups were compared using an analysis of covariance (ANCOVA) model (with possible covariate adjustment). Furthermore, a mixed model was applied taking into account all available data.

Evaluation of healthcare resource utilization: Frequency tabulation (N and %) by treatment group of prior antipsychotic medication (used for at least 4 weeks during the 12 month retrospective period, including the 4 weeks immediately prior baseline), new oral antipsychotic treatment initiated at baseline, other antipsychotic treatments, and concomitant medications (with categories "antidepressants –any" and "mood stabilizers –any") were provided.

A frequency tabulation (N and %) by period and by treatment group whether patients visited any health care providers for psychiatric reasons was presented per time interval for each type of provider. These frequencies were analyzed by Poisson negative binomial regression.

Frequency tabulation was made of the number and percentage of patients in each treatment group that were hospitalized at baseline – overall and subdivided by type (full, partial) and by reason (psychiatric, social, and other). In addition, descriptive statistics (N, mean, standard deviation, median and range) for the total length of hospitalization in each 3-month period subdivided by type (full, partial) and by reason (psychiatric, social, and other) were provided. The hospitalization frequencies were analyzed by Poisson negative binomial regression. Length of hospitalization was analyzed in a non-parametric way using Van Elteren tests.

Time to first hospitalization was graphically and descriptively presented by Kaplan-Meier estimates and further analyzed by means of a logrank test and Cox-regression.

Treatment satisfaction: Tabulation (N and %) of the scores at all time intervals by period and by treatment group was performed, as well as cross-tabulation versus (vs.) baseline was performed as well. Descriptive statistics by period and by treatment group at all time intervals were presented for actual values and the changes from baseline. Changes from baseline were to be analyzed by means of ANCOVA and mixed models.

Evaluations of Patient Characteristics: For body weight and body mass index (BMI) descriptive statistics of the actual values and the changes from baseline at all time intervals were provided by period and by treatment group. Changes from baseline were analyzed by means of ANCOVA and mixed models. Abnormal weight changes vs. baseline were tabulated. For employment and living status, frequency tabulations by period and by treatment group of current employment status and current living status at each time interval were shown. Furthermore, cross-tabulations vs. baseline of employment status (only the additional 'working/student' vs. 'not working' category) and living status was produced. For substance abuse, frequency tabulations by period and by treatment group of substance abuse during the 4 weeks prior to the visit were provided for each time interval. Furthermore, cross-tabulations vs. baseline were provided for the different time intervals.

Safety Evaluations: The original terms used in the electronic case report forms by investigators to identify ADRs/AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 11.0. Adverse drug reactions occurring during the 12 months prior to baseline (retrospective period) and AEs during the prospective period were recorded.

RESULTS

1. STUDY POPULATION

Study Completion/Withdrawal Information:

Overall, 3,029 patients were enrolled in this study. All 3,029 enrolled patients were included in the safety analysis set, while 3006 patients (excluding 23 protocol violators) were included in the intent-to-treat (ITT) analysis set for analysis of effectiveness. Unless indicated otherwise, data referred to throughout this document are for the ITT analysis set (ie, excluding the 23 protocol violators). Of the 3,006 patients in the ITT analysis set, 2,521 (83.9%) completed the study through Month 12, and 485 (16.1%) discontinued the study. The proportion of patients who discontinued study treatment was comparable between the paliperidone ER group (16.2%) and the all other antipsychotics group (16.0%). The most common reason for discontinuation was 'lost of follow-up' (8.4% of all patients) (Table 2).

Table 2: Number of Patients Ongoing/Completed/Discontinued
(Paliperidone ER vs. All Other Antipsychotics) (ITT Analysis Set)

	Paliperidone ER			All other		
	N	% (1)	% (2)	N	% (1)	% (2)
Study completed	1,847	83.8%	.	674	84.0%	.
Discontinued study	357	16.2%	.	128	16.0%	.
Withdrawal of consent	82	3.7%	23.0%	22	2.7%	17.2%
Lost of FU	176	8.0%	49.3%	77	9.6%	60.2%
Lack of compliance	22	1.0%	6.2%	4	0.5%	3.1%
Death	14	0.6%	3.9%	2	0.2%	1.6%
Other	63	2.9%	17.6%	23	2.9%	18.0%
Reason Missing	0	0.0%	0.0%	0	0.0%	0.0%

Protocol Deviations:

Of the 3,029 enrolled patients, 23 patients were classified as protocol violators. All 23 protocol violators belonged to the all other antipsychotics group.

Demographic and Baseline Characteristics:

Demographic (Attachment 4) and other baseline characteristics (Attachment 5) were comparable between the paliperidone ER group and the all other antipsychotics group.

The mean (±SD) age of patients in the ITT analysis set was 38.4 (±12.2) years. Most (±54.9%) patients were male.

Antipsychotic Treatment at Baseline:

Mean daily starting dose of paliperidone ER at baseline was 6.32 (±2.40) mg. The range of the daily starting dose of paliperidone ER at baseline was 3 to 24 mg (Attachment 6).

The daily mean modal dose of paliperidone ER during the entire treatment course was 7.62 (±2.94) mg. The range of modal dose of paliperidone ER was 3 to 27 mg/day (Table 3).

Table 3: Distribution of Modal Dose During the Entire Treatment Course by Antipsychotic
(ITT Analysis Set)

	N patients		Distribution Modal Dose (in mg)						
Antipsychotic	N	%	Mean	Std	Min	P 25	Median	P 75	Max
Paliperidone ER	2,203	73%	7.62	2.94	3	6	6	9	27
Amisulpride	66	2%	605.61	359.54	30	400	400	800	1,600
Aripiprazole	124	4%	16.41	7.88	3	10	15	20	45
Olanzapine	116	4%	14.93	6.74	3	10	15	20	40
Quetiapine	152	5%	476.97	304.63	25	250	400	600	1,600
Risperidone	188	6%	4.65	2.72	1	2	4	6	12
Ziprasidone	70	2%	121.71	61.36	40	80	120	160	240

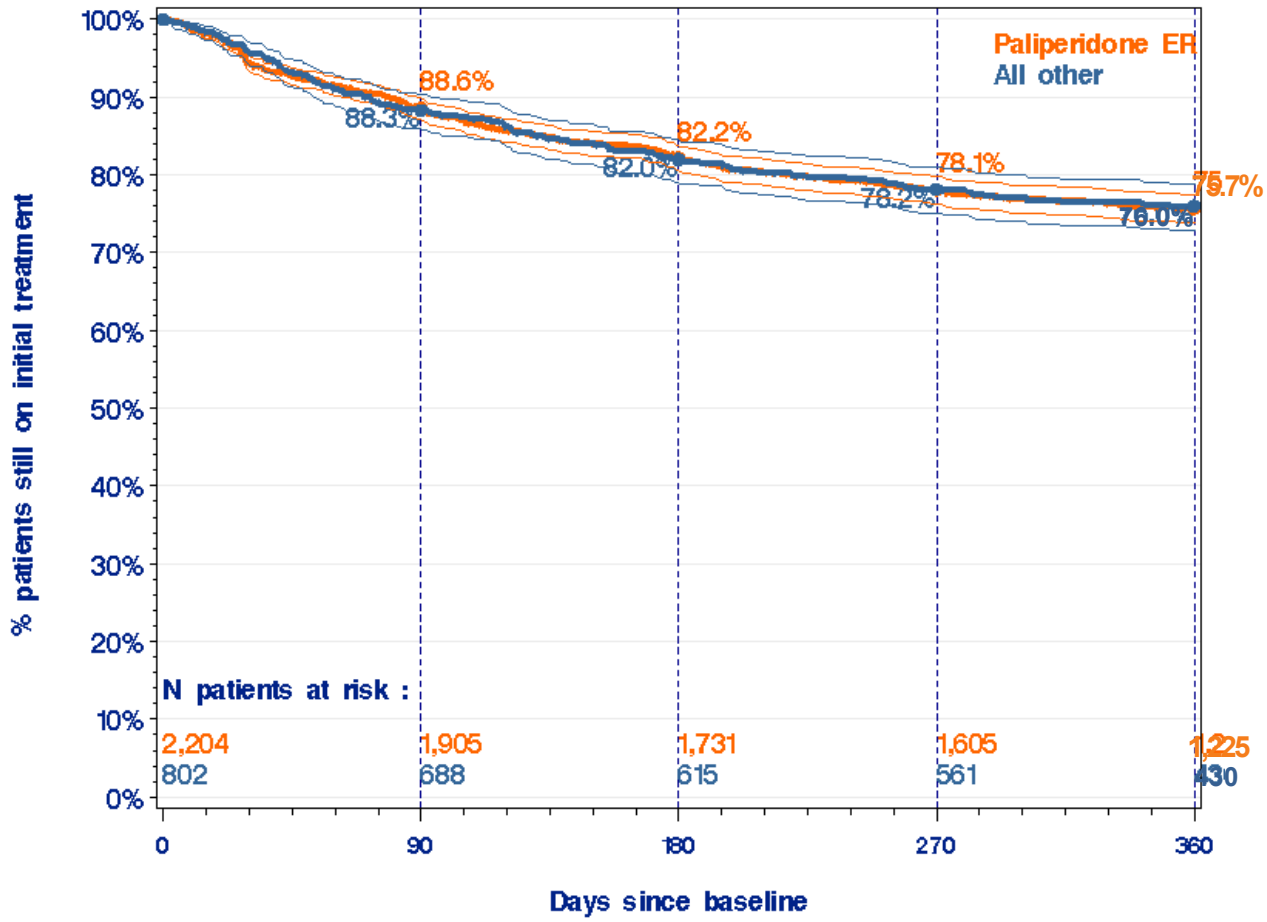
There was no apparent difference between treatment groups in the distribution of antipsychotic use in the retrospective year (Attachment 7).

2. Evaluations of Clinical Effectiveness

Time to Discontinuation of Initial Treatment:

Figure 1: Time on Initiated Treatment (Kaplan-Meier Curve Including 95% Confidence Intervals): Paliperidone ER vs. All Other Antipsychotics

(ITT Analysis Set, Dropout = Censored, All Patients)



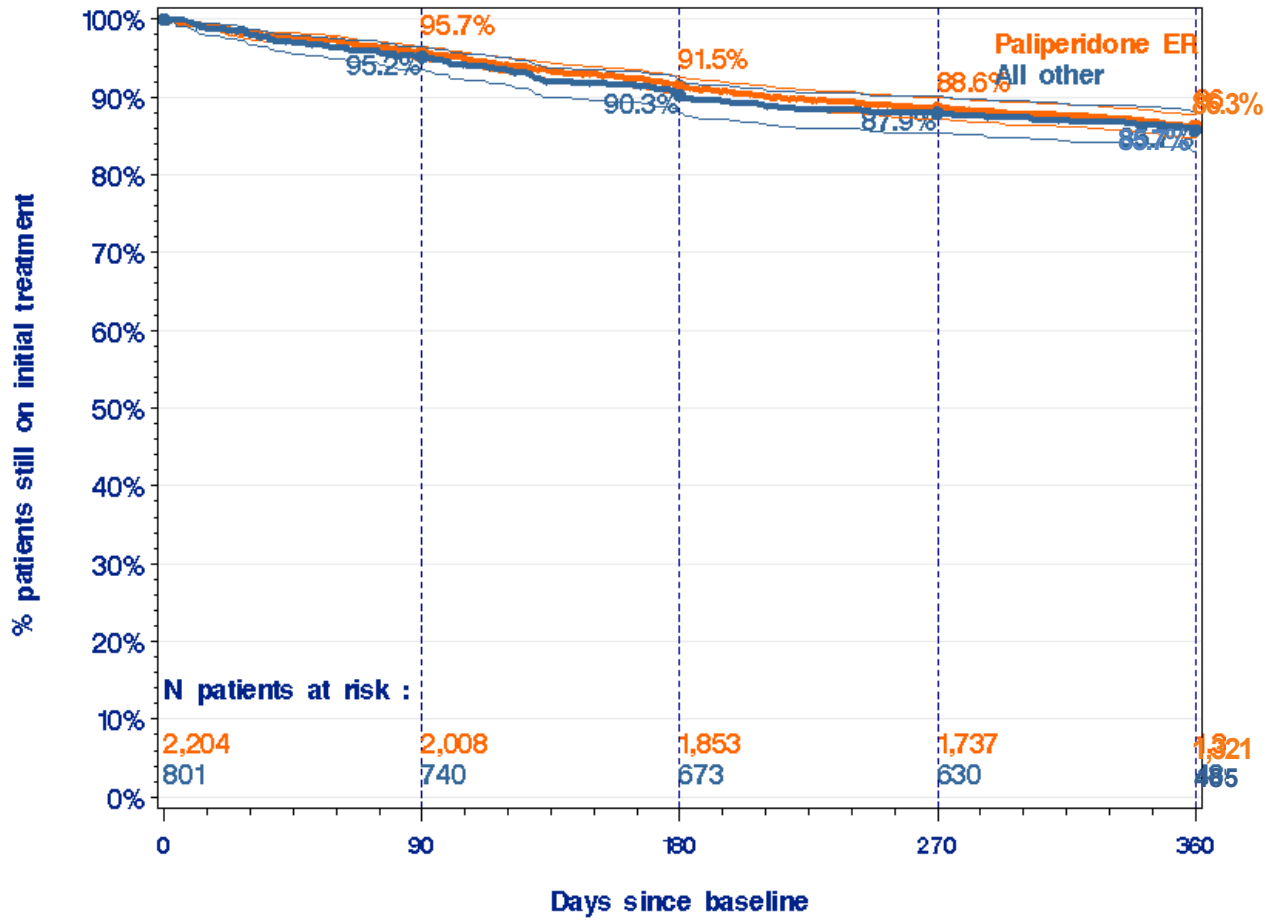
The proportion of patients still on treatment after 1 year follow-up was 75.7% in the paliperidone ER group and 76.0% in the all other antipsychotics group. The difference between groups was not statistically significant (Hazard ratio [HR] = 1.05 [0.89, 1.25]; p-value = 0.5364) (Figure 1). In the primary analysis, patients discontinuing the study were censored at the time of study drop-out. When considering study drop-outs as study discontinuations, the proportion of patients still on treatment after 1 year was 69.0% in the paliperidone ER group and 66.3% in the all other antipsychotics group (HR = 0.92; p=0.22).

Post-hoc analysis on the primary endpoint showed that the difference in time to treatment discontinuation was more substantial in the subgroup of polytherapy patients; the proportion of patients still on treatment after 1 year was 76.4% for the paliperidone ER group and 73.1% for the all other antipsychotics group (HR=0.89 [0.66, 1.21]; p=0.4536). When considering study drop-outs as treatment discontinuations, the proportion of patients still on treatment after 1 year was 71.0% and 64.5% for the paliperidone ER and all other antipsychotics groups respectively (HR=0.78 [0.61, 1.01]; p=0.0633). When adjusting for baseline co-variates, the difference in time to treatment discontinuation increases and becomes statistically significant (HR=0.69 [0.51-0.93]; p=0.0148).

Time to Hospitalization

Figure 2: Time to Hospitalization (Kaplan-Meier Curve Including 95% Confidence Intervals): Paliperidone ER vs. All Other Antipsychotics

(ITT Analysis Set, All Patients)



The proportion of patients without hospital admission at 1 year after treatment initiation was similar between treatment groups (86.3% in the paliperidone ER group and 85.7% in the all other antipsychotics group; HR = 0.95 [0.76, 1.19]; p value = 0.6677; not significant [NS]) (Figure 2).

Comparison of Hospitalization in the Prospective vs. Retrospective Period (Pre- vs. Post Analysis)

Pre- versus post analysis of the percentage of patients hospitalized showed a reduction in the paliperidone ER group (pre-baseline 31% vs. postbaseline 27%) and the all other antipsychotics group (pre-baseline 33% vs. postbaseline 32%). The small difference in the reduction of hospitalized patients postbaseline between the paliperidone ER and all other antipsychotics groups was not statistically significant (p=0.2941; NS) (Attachment 8).

Pre- versus post analysis of number of hospital days showed a reduction in mean number of hospital days by 0.73 days (pre-baseline 17.21 days vs. postbaseline 16.48 days) for the paliperidone ER group compared with a reduction of 0.23 days (pre-baseline 20.08 days vs. postbaseline 19.85 days) for the all other antipsychotics group. The difference of 0.5 days in the reduction in mean number of hospital days between groups was statistically significant (p<0.0180) (Attachment 10).

Pre- versus post analysis on number of hospital admissions did not show significant differences between the paliperidone ER and the all other antipsychotics groups (Attachment 11).

Clinical Global Impression-Severity

There was a decreasing trend in mean/median CGI-S score from baseline to Visit 4 across all treatment groups. The decreases in mean and median CGI-S scores from baseline to Visit 4 were comparable between the paliperidone ER and all other antipsychotics group. The decrease in mean CGI-S score across treatments ranged from 1 to 1.5, with paliperidone ER yielding a mean decrease of 1.2. Evolution over time was not different for paliperidone ER (from 4.1 at baseline to 2.9 at 12 months) compared with the all other antipsychotics group (from 4.2 at baseline to 3.1 at 12 months), based on a mixed model. CGI-S improvement over time was significantly less pronounced for quetiapine (from 4.1 at baseline to 3.1 at 12 months) (mixed model: p=0.0020).When last observations were carried forward for patients who withdrew treatment prior to Visit 4 the trend of decrease in mean/median CGI-S score from baseline was retained for all antipsychotics including paliperidone ER (Attachment 12).

Personal and Social Performance Scale

There was an increasing trend in mean/median PSP score indicating improvement in level of functioning from baseline to Visit 4 across all treatment groups. The increase in mean and median PSP score from baseline to Visit 4 was comparable for the paliperidone ER and all other antipsychotics groups. Increases in mean PSP score across treatments ranged from 8.9 to 19.3, with paliperidone ER yielding a mean increase of 15.3. Evolution over time was not different for the paliperidone ER group (from 53.4 at baseline to 68.7 at 12 months) compared with the all other antipsychotics group (from 52.0 at baseline to 66.2 at 12 months), based on a mixed model. When last observations were carried forward for patients who withdrew treatment prior to Visit 4, the trend of increase in mean/median score from baseline was retained for all antipsychotics including paliperidone ER (Attachment 13).

SF12

SF12-Physical

The mean and median physical component score of the SF12 health survey increased across all treatments from baseline to end of treatment, indicating improvement in physical well being of the patients. The increase in mean PCS was significantly higher for the paliperidone ER group than for the all other antipsychotics group (4.0 vs. 3.1) (mixed model: p=0.0060). The increases in mean PCS across treatments ranged from 1.9 to 4.1, with paliperidone ER yielding a mean increase of 4.0 (Attachment 14).

SF-12-Mental

The mean and median mental component score of the SF12 health survey increased across all treatments from baseline to end of treatment, indicating improvement in mental well being of the patients. The increase in mean MCS was comparable between the paliperidone ER group and the all other antipsychotics group (7.4 vs. 7.1) (mixed model; NS). The increases in mean MCS across treatments ranged from 4.0 to 9.9, with paliperidone ER yielding a mean increase of 7.4 (Attachment 15).

Visual Analogue Scale

Quality of Sleep: Visual Analogue Scale

The mean and median quality of sleep VAS score increased across all treatments from baseline to Visit 4, indicating improvement in sleep quality of the patients. The increase over time was comparable between the paliperidone ER group (from 58.8 at baseline to 77.0 at 12 months) and the all other antipsychotics group (from 56.8 at baseline to 75.9 at 12 months) (mixed model: NS). The increases in mean score ranged from 11.6 to 25.2, with paliperidone ER yielding a mean increase of 18.2. When last observations were carried forward for patients who withdrew before Visit 4, the increase in mean and median score was retained across all treatments (Attachment 16).

Daytime Drowsiness: Visual Analogue Scale

The mean and median daytime drowsiness VAS score decreased across all treatments from baseline to Visit 4, indicating improvement in patient condition. The decrease in mean daytime drowsiness VAS score was comparable between the paliperidone ER group (from 38.9 at baseline to 22.6 at 12 months) and the all other antipsychotics group (from 40.3 at baseline to 24.6 at 12 months) (mixed model, NS). The decreases in mean score ranged from 12.3 to 20.0, with paliperidone ER yielding a mean decrease of 16.3. When last observations were carried forward for patients who withdrew before Visit 4, the decrease in mean and median score was retained across all treatments including paliperidone ER (Attachment 17).

Treatment Satisfaction

The mean and median treatment satisfaction score increased across all treatments from baseline to end-of-treatment, indicating improvement. The increase in mean treatment satisfaction score was comparable between the paliperidone ER group (from 3.7 at baseline to 5.1 at 12 months) and the all other antipsychotics group (from 3.6 at baseline to 5.0 at 12 months). The increases in mean scores ranged from 1.1 to 1.6, with paliperidone ER yielding an increase of 1.4. The median score also improved across all treatment groups including paliperidone ER (Attachment 18).

Percentage of Patients with Concomitant Medications

There was a decreasing trend from baseline to Visit 4 in the percentage of patients with any concomitant medications, which was numerically higher for the paliperidone ER group (13.5% decrease; from 66.9% at baseline to 53.4% at 12 months) than for the all other antipsychotics group (9.3% decrease; from 67.9% at baseline to 58.6% at 12 months). When last observations were carried forward for patients who withdrew prior to Visit 4, the decreasing trend was retained and the decrease from baseline to last observation carried forward (LOCF) remained numerically higher for the paliperidone ER group (12.3%) than for the all other antipsychotics group (9.3%) (Attachment 19).

Percentage of Patients with Outpatient Visits

The percentage of patients with outpatient visits by 3-monthly periods showed a decreasing trend from baseline to Visit 4, which was numerically higher for the paliperidone ER group (17.5% decrease; from 80.1% at baseline to 62.6% at 12 months) than for the all other antipsychotics group (15.6% decrease; from 77.9% at baseline to 62.3% at 12 months). When last observations were carried forward for patients who withdrew prior to Visit 4 the decreasing trend was retained. Upon LOCF, the decreases in percentage of patients with outpatient visits from baseline to Visit 4 ranged from 6.0% to 18.6%, with paliperidone ER yielding a decrease of 16.1%. The decrease with paliperidone ER (16.1%) was numerically higher than for the all other antipsychotics group (14.2%) (Attachment 20).

Evaluation of Patient Characteristics

The mean increase in BMI over 12 months was comparable for the paliperidone ER group (from 25.8 kg/m^2 at baseline to 26.3 kg/m^2 at 12 months) and the all other antipsychotic group (from 25.9 kg/m^2 at baseline to 26.7 kg/m^2 at 12 months) during the prospective period of the study (Attachment 21). There was a trend of increase in mean body weight from baseline to Visit 4 across all treatment groups. The mean increase in weight from baseline over 12 months was numerically lower in the paliperidone ER group (from 74.1 kg at baseline to 78.8 kg at 12 months) than in the all other antipsychotics group (74.1 kg at baseline to 80.5 kg at 12 months), but the difference did not reach statistical significance (Attachment 22). The mean increase in BMI and weight was significantly lower in patients newly initiated on paliperidone ER compared with patients initiated on olanzapine (mean increase in BMI of 0.5 kg/m^2 vs. 2.0 kg/m^2; $p<0.0001$ and mean increase in weight of 4.7 kg vs. 10.7 kg; $p=0.006$).

The proportion of patients with abuse of tobacco, alcohol, cannabis or any other substance was similar between the paliperidone ER group and the all other antipsychotics group during the prospective period of

the study. There was a slight reduction in the number of patients with substance abuse across all treatment groups (Attachment 23 and Attachment 24).

3. SAFETY

An overall summary of the incidence of ADRs (retrospective period) and AEs (prospective period) is presented in Attachment 26. The type of ADRs and AEs in the respective periods is summarized by system organ class (SOC) and treatment in

Attachment 27.

During the retrospective period of the study, 699 (23.1%) patients experienced at least 1 ADR, 33 (1.1%) patients experienced at least 1 SADR, and 108 (3.6%) patients experienced at least 1 severe ADR. The overall incidences of all ADRs, SADRs, and severe ADRs were comparable between the paliperidone ER and all other antipsychotics groups (see Table 4).

Table 4: Adverse Drug Reactions Documented During the Retrospective Period

(Safety Analysis Set)

Number of patients	Paliperidone ER	All other antipsychotics
With at least one ADR	23.5%	21.8%
With at least one serious ADR	1.0%	1.3%
With at least one severe ADR	3.4%	4.1%

ADR: adverse drug reaction
ER: extended release
Source: Attachment 25

The ADRs of weight increased (3.3%), schizophrenia (3.2%), extrapyramidal disorder (2.4%), and somnolence (2.2%) were the most common individual ADRs documented in the retrospective period of the study.

During the prospective period of the study, 947 (31.3%) patients experienced at least 1 AE, 350 (11.6%) patients experienced at least 1 SAE, and 159 (5.2%) patients experienced at least 1 severe AE. The overall incidence of AEs was numerically higher in the paliperidone ER group than in the all other antipsychotics group. The overall incidences of all SAEs and severe AEs were comparable between the paliperidone ER group and the all other antipsychotics group (see Table 5).

Table 5: Adverse Events Reported During the Prospective Period

(Safety Analysis Set)

Number of patients	Paliperidone ER	All other antipsychotics
With at least one AE	32.0%	29.3%
With at least one SAE	11.7%	11.3%
With at least one severe AE	5.3%	5.2%

AE: adverse event
ER: extended release
SAE: serious adverse event
Source: Attachment 25

The AEs of schizophrenia, insomnia, weight increased, extrapyramidal disorder, psychotic disorder and somnolence were the most common AEs (ie, ≥2% in any treatment group) documented during the prospective period of the study (see Table 6).

Table 6: Type of Adverse Events Reported by ≥2% of Patients in Any Treatment Group During the Prospective Period

(Safety Analysis Set)

Body System Preferred Term	**Paliperidone ER**	**All other antipsychotics**
Psychiatric disorders	**19.1%**	**17.9%**
Schizophrenia	8.5%	5.6%
Psychotic disorder	1.9%	2.9%
Insomnia	2.5%	2.7%
Nervous system disorders	**10.0%**	**9.5%**
Extrapyramidal disorder	2.1%	1.6%
Somnolence	1.5%	2.5%
Investigations	**2.9%**	**3.3%**
Weight increased	2.3%	3.0%

ER: extended release

Source: Attachment 26

There were 16 deaths (16/3,029 patients; 0.53%) reported during the prospective period of the study (see Table 7). The number of deaths was numerically higher in the paliperidone ER group (14/2,204 patients; 0.64%) than in the all other antipsychotics group (2/825 patients; 0.24%). For all patients in the paliperidone ER group, the cause of death was considered either not related (10/14; 71%) or doubtfully related (4/14; 29%) to the prescribed medication. For the 2 deaths in the all other antipsychotics group, the cause of death was considered not related to the individual prescribed antipsychotics. Review of the available data on a case-by-case basis and careful exploration of the individual causes of death did not reveal any commonalities between cases or a safety signal.

Table 7: List of Deaths During the Prospective Period

(Safety Analysis Set)

eCRF Id	Group	Preferred Term	Outcome	Causality
00489	Paliperidone ER	Death	Death	Not Related
00524	Paliperidone ER	Accidental Death	Death	Not Related
00566	Paliperidone ER	Gastrointestinal Hemorrhage	Death	Doubtful
01684	Paliperidone ER	Sudden Death	Death	Not Related
01795	Paliperidone ER	Asthenia	Death	Not Related
		Body Temperature Increased	Death	Not Related
		Brain Edema	Death	Not Related
		Diet Refusal	Death	Not Related
		Dyspnea	Death	Not Related
01824	Paliperidone ER	Cerebral Circulatory Failure	Death	Doubtful
		Hypertension	Death	Doubtful
01978	Paliperidone ER	Fall	Death	Not Related
02011	Paliperidone ER	Pulmonary Embolism	Death	Not Related
02430	Paliperidone ER	Drug Abuse	Death	Not Related
02970	Paliperidone ER	Head Injury	Death	Not Related
		Death	Death	Not Related
03567	Paliperidone ER	Asphyxia	Death	Doubtful
04035	Paliperidone ER	Cardiac Failure	Death	Not Related
04110	Paliperidone ER	Completed Suicide	Death	Doubtful
04150	Paliperidone ER	Completed Suicide	Death	Not Related
03219	All Other Antipsychotics Group	Intracranial Hematoma	Death	Not Related
03360	All Other Antipsychotics Group	Death	Death	Not Related

eCRF: electronic case report forms
ER: Extended Release
Source: Attachment 27

CONCLUSIONS

- The effect of paliperidone ER on time to discontinuation, overall severity of symptoms, personal and social performance, health related quality of life (mental component), quality of sleep, and healthcare utilization was similar as compared to all other antipsychotics combined.
- Improvement in the physical component of the SF12 score and reduction in mean number of hospital days was significantly better with paliperidone ER treatment than for all other antipsychotics combined.
- A post-hoc analysis on a subgroup of patients treated with polytherapy showed lower discontinuation and hospitalization rates with paliperidone ER compared with all other antipsychotics.
- Paliperidone ER was generally safe and well tolerated. The safety profile in this studywas similar to that in previous randomized controlled clinical trials with paliperidone ER.
- In this study there were some differences in effectiveness between paliperidone ER and individual oral antipsychotics, supporting available evidence in the literature that atypical antipsychotics do not represent a homogenous class of drugs but rather a heterogeneous group of medications with different properties.

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