SYNOPSIS

Issue Date: 12 March 2010
Document No.: EDMS-PSDB-8872243:3.0

Name of Sponsor/Company	Janssen-Cilag International N.V.
Name of Finished Product	INVEGA®
Name of Active Ingredient(s)	Paliperidone ER

Protocol No.: R076477SCH3018

Title of Study: Tolerability, Safety and Treatment Response of Flexible Doses of Paliperidone Extended Release (ER) in Acutely Exacerbated Subjects with Schizophrenia (PERTAIN)

Study Name: PERTAIN

EudraCT Number: 2006-006642-34

Principal Investigator: not applicable

Publication (Reference): not applicable

Study Period: 4 July 2007 – 14 May 2009

Phase of Development: 3

Objectives:

Primary Objective: To explore the response to flexible doses of paliperidone ER in acutely exacerbated subjects with schizophrenia (response was defined as a decrease of at least 30% in total Positive and Negative Syndrome Scale [PANSS] score from baseline to endpoint).

Secondary Objectives: To explore efficacy, tolerability, disease severity, functioning, and treatment satisfaction. This was done by:

- assessing the efficacy on psychotic symptoms (PANSS total score and subscores);
- assessing the proportion of subjects improving ≥ 20%, ≥ 40%, and ≥ 50% in total PANSS from baseline to endpoint;
- exploring the onset of efficacy of flexible doses of paliperidone ER (as measured by individual subject's change in total PANSS score between study visits);
- assessing disease severity (Clinical Global Impression – Severity [CGI-S]);
- assessing personal and social functioning (Personal and Social Performance scale [PSP)];
- assessing quality of sleep and daytime drowsiness (11-point categorical evaluation scale);
- assessing treatment satisfaction (5-point categorical evaluation scale);
- assessing extrapyramidal symptoms (EPS) (Abnormal Involuntary Movement Scale [AIMS], Simpson-Angus Extrapyramidal Symptoms Rating Scale [SAS], and Barnes Akathisia Rating Scale [BARS]);
- assessing side effects profiles by means of physical examination, body weight, vital signs, and adverse events (AEs).

Methods: This was an open-label, single arm, 6-week study conducted at multiple sites in Europe and Israel that evaluated tolerability, safety, and efficacy of flexibly dosed paliperidone in subjects with schizophrenia who were admitted for an acute exacerbation of their disease. The planned total sample size was approximately 300 subjects with a diagnosis of schizophrenia suffering from an acute episode. Hospitalization was mandatory for the first 7 days of the study. Throughout the study flexible dosing in a range of 3 to 12 mg/day could be used. Flexible dosing allowed investigators to adjust the dosage of each subject as clinically indicated. In general, the recommended paliperidone ER dose was 6 mg once daily. Some subjects could benefit from higher or lower doses in the recommended dose range of 3 to 12 mg once daily. All raters at an investigational site had to be trained and certified (for PANSS). Subjects who completed this 6-week study and responded well and who liked to continue paliperidone ER treatment were eligible to be enrolled in an extension phase until paliperidone ER was available in the respective country. However, the extension phase lasted maximally 12 months after the last subject had completed the 6-week core treatment phase or earlier in case the sponsor would decide to stop the development and/or the registration of the product. Subjects received, without cost, paliperidone ER. During the extension period, only AE- and serious adverse event (SAE)-reporting and body weight measurement was performed. No efficacy or other assessments were performed during the extension phase.

Statistical analysis took place after all subjects had completed the 6-week core treatment phase and also at the end of the extension phase. An interim analysis was performed when 100 subjects had completed the 6-week core treatment phase. All medications (prescriptions or over-the-counter medications) continued at the start of the study or started during the study and different from the study medication, had to be documented on the Concomitant Therapy Form of the CRF. Neuroleptics and other psychotropic medication that had been administered prior to study started for reasons other than the disease itself, e.g., sleep induction or sedation could be continued during the study but the dose had to be kept stable. Other neuroleptics than paliperidone ER for the treatment of schizophrenia were not allowed during this study. Any previous antipsychotics had to be tapered off according to clinical practice, preferably within the first few days of the study. The following benzodiazepines were allowed during the study but not for a period longer than 10 consecutive days: lorazepam (up to 6 mg/day) or diazepam (up to 30 mg/day). Benztropine mesylate or biperidene up to 4 mg/day or trihexyphenidyl up to 10 mg/day could be used for the treatment of EPS. Benzodiazepines, administered as mentioned above, were allowed for treatment or akathisia. Prior to the use of treatment for EPS, AIMS, BARS, and SAS had to be performed and scores had to be documented. The investigator had to reevaluate the need for anticholinergic medication on an ongoing basis.

Any changes in dosages had to be documented in the Concomitant Therapy Form of the CRF. For any concomitant therapy given as a treatment for a new condition or a worsening of an existing condition, the condition had to be documented on the AE Form of the CRF. For further information on concomitant therapies, please refer to the European Medicines Agency (EMEA) approved Summary of Product Characteristics (SmPC) in Attachment 9 of the Clinical Trial Protocol (CTP).

Number of Subjects (Planned and Analyzed):

	N
Planned	300
Enrolled (all treated subjects)	294
Interim analysis	
All subjects	100
Intent-to-treat	100
Final analysis (6-week study)	
All subjects	294
Intent-to-treat[a]	294
Safety[b]	294
Efficacy[c]	294
Per protocol[d]	243
Final analysis (extension phase)	
Safety[e]	139

[a] All subjects who received paliperidone ER at least once were included in the analysis of demographic and baseline characteristic data.
[b] All subjects who received at least one dose of paliperidone ER and provided any post-baseline safety information were included in safety data analyses.
[c] All subjects who received at least one dose of paliperidone ER and provided any post-baseline efficacy measurement were included in efficacy data analyses.
[d] All subjects included in the intent-to-treat data analyses except those for whom a major protocol deviation was reported.
[e] All subjects who entered the extension phase and received paliperidone ER at least once during the extension and provided at least one safety measurement during the extension phase.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria: Subjects enrolled in this study were required to meet the following acceptance criteria:

- Subject met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for schizophrenia.
- Male or female, aged ≥ 18 years.
- Subject had to be experiencing an acute schizophrenic episode with a PANSS total score at baseline ≥ 70.
- Subject had to be admitted to hospital for treatment of the acute schizophrenic episode and had to agree for voluntary hospitalization for at least the first 7 days of the study.
- Subjects or their legally acceptable representatives had to have signed an informed consent document indicating that they understood the purpose of and procedures required for the study and were willing to participate in the study.
- Female subjects had to be postmenopausal (for at least 1 year), surgically sterile, abstinent, or, if sexually active, be practicing effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch, male partner sterilization) before entry and throughout the study. Female subjects of child-bearing potential had to have a negative urine pregnancy test at screening.

Diagnosis and Main Criteria for Inclusion, cont'd:

Exclusion Criteria: Subjects were not to be enrolled into the study if it was determined upon prestudy examination that:

- This was their first antipsychotic treatment ever.
- They were on clozapine or a long-acting injectable antipsychotic during the last 3 months.
- They had a relevant history of any significant and/or unstable cardiovascular, respiratory, neurologic (including seizures or significant cerebrovascular), renal, hepatic, endocrine, or immunologic diseases, including recent or present clinically relevant laboratory abnormalities (as deemed by the investigator).
- They had a known clinically relevant abnormal laboratory values or electrocardiogram (ECG).
- They had a history or current symptoms of tardive dyskinesia.
- They had a history of neuroleptic malignant syndrome.
- They were judged to be at high risk for or presence of violence or self-harm.
- They were pregnant or breast-feeding female.
- They had received an experimental drug or used an experimental medical device within 30 days before the planned start of treatment.
- They had a narrowing or blockage of their gastro-intestinal tract.
- They were unable to swallow the study medication whole with the aid of water (subjects could not chew, divide, dissolve, or crush the study medication, as this could affect the release profile).
- They had a current or known history (over the past 6 months) of substance dependence according to DSM-IV criteria.
- They were employees of the investigator or study center, persons with direct involvement in the proposed study or other studies under the direction of that investigator or study center, or family members of the employees or the investigator.
- They had a known hypersensitivity to paliperidone ER or risperidone.

Test Product, Dose and Mode of Administration, Batch No.:

Study Medication	Batch Number	Expiry Date
Paliperidone ER 12-mg tablet kits	0602596 7AG1026-X 7AG1026-X	29/02/08 31/01/09 31/01/10[a]
Paliperidone ER 3-mg and 6-mg tablet kits	0620766 (3-mg tablets) 0620769 (3-mg tablets) 0716337 (3-mg tablets) 0729774 (3-mg tablets) 0617714 (6-mg tablets) 0707704 (6-mg tablets) 0729777 (6-mg tablets)	31/08/08 31/08/08 31/10/08 31/10/10 30/06/08 30/11/08 31/10/10
Paliperidone ER 3-mg, 6-mg, and 9-mg tablet kits	0620766 (3-mg tablets) 0617714 (6-mg tablets) 0602601 (9-mg tablets)	31/08/08 30/06/08 30/04/08

[a] expiry date extended with 12 months

Duration of Treatment: 6 weeks of flexible dosing (paliperidone ER at a daily dose of 3-12 mg); subjects who completed this 6-week study and responded well and who would like to continue paliperidone ER treatment, were eligible to be enrolled in an extension phase until paliperidone ER was available in the respective country (this extension phase lasted maximally 12 months after the last subject completed the 6-week core treatment phase or earlier in case the sponsor decided to stop the development and/or the registration of the product).

Criteria for Evaluation:

Efficacy Procedures:	- The PANSS was assessed at all visits during the treatment phase (i.e., Visits 1 to 9, and in case of early discontinuation). - The PSP and CGI-S scales, and the sleep quality and daytime drowsiness were evaluated at Visits 1, 6, 7, 8, and 9, and in case of early discontinuation. - Treatment satisfaction was assessed at Visit 9 and in case of early discontinuation.
Safety Procedures:	- The EPS rating scales AIMS, BARS, and SAS were assessed at Visits 1, 6, 7, and 9, and in case of early discontinuation. - Vital signs were measured at all visits (i.e., Visits 1 to 9) and in case of early discontinuation. - Body weight was assessed at Visit 1 and 9 and in case of early discontinuation (and at every visit during the extension phase). - AEs were monitored continuously from signing of the Informed Consent Form (ICF) until the last study-related activity (also during the extension phase). - A urine pregnancy test was performed at Visits 1, 9 and in case of early discontinuation.

Statistical Methods: Descriptive statistics, frequency tabulations, ITT analysis, Wilcoxon signed rank tests

RESULTS:

STUDY POPULATION:

In total, 295 subjects were screened. One of these subjects was excluded from the intent-to-treat (ITT) population because no study medication was taken due to substance dependence. Two hundred and ninety-four (294) subjects entered the core treatment phase of this open-label trial and started treatment with paliperidone ER (flexible dosing in a range of 3-12 mg/day).

The majority of the 294 subjects included in the ITT population (80%) completed the 6-week core treatment phase, whereas 20% of subjects prematurely discontinued the trial. Reasons for premature discontinuation are summarized below. The main reasons for discontinuation were subject's choice (9%) and lack of efficacy (6%).

Study Completion/Withdrawal Information
(Study R076477SCH3018: *ITT-Population*)

N (%)	Total N = 294
Completed the Core Treatment Phase	**234 (79.6)**
Withdrawn, Reason	**60 (20.4)**
Subject choice (subject withdrew consent)	26 (8.8)
Lack of efficacy	18 (6.1)
AE	9 (3.1)
Lost to follow-up	4 (1.4)
Other[a]	3 (1.0)
Entered the Extension Phase	**139 (59.4)**
	Total N = 139
Completed the Extension Phase (up to maximum 12 months)	**57 (41.0)**
Withdrawn, Reason	**82 (59.0)**
Subject choice (subject withdrew consent)	34 (24.5)
Lack of efficacy	25 (18.0)
AE	11 (7.9)
Lost to follow-up	6 (4.3)
Other	5 (3.6)
Death	1 (0.7)

[a] Including 1 subject who had to be moved to a penitentiary hospital, 1 subject who met exclusion criterion 2 and was therefore discontinued by project management, and 1 subject who was discontinued because his/her symptoms worsened (upon decision of the investigator).

N = total number of subjects

Demographic data collected at screening revealed a population with slightly more male (53%) than female subjects (47%). The mean (standard deviation [SD]) age at baseline was 40.3 (12.4) years.

The mean (SD) age at first diagnosis of schizophrenia was 29.8 (9.8) years. The mean (SD) body weight was 78.8 (17.8) kg, resulting in a mean (SD) body mass index (BMI) of 27.11 (5.35) kg/m².

According to the DSM-IV criteria, most subjects were diagnosed with paranoid schizophrenia (88%). Other subjects were diagnosed with undifferentiated (5%), residual (4%), or disorganized (2%) schizophrenia.

At baseline, the mean (SD) duration since first diagnosis of schizophrenia was 10.9 (9.3) years. The majority of subjects (94%) had been hospitalized due to psychotic symptoms prior to this study. The number of prior hospitalizations ranged from 0 to 51, with a mean (SD) value of 6.9 (7.2). The number of hospitalizations during the 12 months preceding this study ranged from 0 to 12, with a mean (SD) value of 0.8 (1.3).

Demographic Data
(Study R076477SCH3018: *ITT-Population*)

	Total N = 294
Age, years	
N	294
Mean (SD)	40.3 (12.4)
Median	39
Range	(18; 74)
Sex, n (%)	
Male	156 (53.1)
Female	138 (46.9)
Weight, kg	
N	288
Mean (SD)	78.8 (17.8)
Median	76
Range	(42; 174)
Height, cm	
N	286
Mean (SD)	170.1 (9.7)
Median	170
Range	(139; 196)

N = total number of subjects

Baseline Disease Characteristics
(Study R076477SCH3018: *ITT-Population*)

	Total N = 294
Duration since first diagnosis of schizophrenia, years	
N	293
Mean (SD)	10.9 (9.3)
Median	8
Range	(0; 45)
Age at first diagnosis of schizophrenia, years	
N	293
Mean (SD)	29.8 (9.8)
Median	28
Range	(14; 68)
Ever been hospitalized, n (%)	
No	18 (6.1)
Yes	276 (93.9)
Type of schizophrenia, n (%)	
Paranoid (295.30)	260 (88.4)
Disorganized (295.10)	7 (2.4)
Undifferentiated (295.90)	15 (5.1)
Residual (295.60)	12 (4.1)
Course, n (%)	
Episodic with interepisode residual symptoms	177 (60.2)
Episodic with no interepisode residual symptoms	49 (16.7)
Continuous	47 (16.0)
Single episode in partial remission	5 (1.7)
Other or unspecified pattern	6 (2.0)
Not known/ not applicable	10 (3.4)

N = total number of subjects

EFFICACY RESULTS OF THE CORE PHASE:

Primary Efficacy Analysis

The primary objective of this trial was to explore the response to flexible doses of paliperidone ER in acutely exacerbated subjects with schizophrenia. Response was defined as a decrease of at least 30% in PANSS total score from baseline to endpoint of the core phase (i.e. Day 42 or at early withdrawal). Overall, 195 subjects (66%) showed response to treatment with paliperidone ER.

Number of Responders
(Study R076477SCH3018: *Efficacy Analysis Set*)

	Total	95% Confidence Interval	
n (%)	(N = 294)	Lower	Upper
Responder			
Yes	195 (66.3)	60.6	71.7
No	99 (33.7)		

N = total number of subjects; n = total number of subjects who showed (no) response

Secondary Efficacy Analysis:

- **Positive and Negative Syndrome Scale for Schizophrenia**

The mean (SD) total PANSS score at baseline was 100.2 (17.2). As of the day after first paliperidone ER intake (Day 2), the observed decrease of the mean total PANSS score was statistically significant ($p<0.0001$) with a mean score of 97.9 at Day 2. Improvements in condition judging from further decreases in PANSS total score were seen at all following time points and all were statistically significant ($p < 0.0001$). After 6 weeks of treatment (Day 42), the mean (SD) total PANSS score had decreased to 68.3 (17.3), corresponding to a mean decrease of 32.1 (17.5). At endpoint, the mean (SD) total PANSS score was 72.7 (20.3), which still corresponded to a mean decrease of 27.5 (20.1) versus baseline. Similar trends of improvement in PANSS score from Day 2 onwards were observed in all PANSS subscales (total positive subscale, total negative subscale, and total general psychopathology subscale).

PANSS Total Score: Actual Values (Study R076477SCH3018: *Efficacy Analysis Set*)

		N	Mean	Median	SD	Minimum	Maximum	95% CI Lower	95% CI Upper
PANSS total score	Visit								
	1: Day 1	294	100.2	98	17.2	70	156	98.2	102.2
	2: Day 2	294	97.9	96	17.2	64	156	95.9	99.9
	3: Day 3	287	94.3	92	17.2	55	156	92.3	96.3
	4: Day 4	288	89.9	89	17.5	50	146	87.8	91.9
	5: Day 5	284	87.1	86	18.5	47	145	84.9	89.2
	6: Day 7	286	82.8	81	19.0	44	143	80.6	85.1
	7: Day 14	276	78.1	77	17.6	38	138	76.0	80.2
	8: Day 28	254	73.1	71	18.3	32	138	70.8	75.3
	9: Day 42	234	68.3	67	17.3	32	133	66.0	70.5
	Endpoint	294	72.7	70	20.3	32	140	70.4	75.1

N = total number of subjects with data

PANSS Total Score: Changes From Baseline (Study R076477SCH3018: *Efficacy Analysis Set*)

		N	Mean	Median	SD	Minimum	Maximum	95% CI Lower	95% CI Upper	p-value[a]
Shift in PANSS total score	Visit									
	2: Day 2	294	-2.3	-1	5.3	-25	18	-2.9	-1.7	< .0001
	3: Day 3	287	-5.8	-4	7.9	-42	17	-6.7	-4.8	< .0001
	4: Day 4	288	-10.3	-8	11.3	-67	18	-11.6	-9.0	< .0001
	5: Day 5	284	-13.3	-11	13.3	-74	24	-14.8	-11.7	< .0001
	6: Day 7	286	-17.4	-15	15.5	-84	30	-19.2	-15.6	< .0001
	7: Day 14	276	-22.3	-21	16.0	-89	36	-24.2	-20.4	< .0001
	8: Day 28	254	-27.2	-26	16.6	-93	25	-29.2	-25.1	< .0001
	9: Day 42	234	-32.1	-31	17.5	-95	7	-34.4	-29.9	< .0001
	Endpoint	294	-27.5	-28	20.1	-95	36	-29.8	-25.2	< .0001

[a] Wilcoxon signed rank test (2-tailed)
N = total number of subjects with data

- **Response Rates:**

In general, at all time points from Day 3 onwards, the percentage of subjects with response in each percentage improvement category increased. At Day 42, after 6 weeks of treatment in the core treatment phase, 88%, 77%, 59%, and 42% of subjects showed at least 20%, 30%, 40%, and 50% response, respectively. At endpoint, at least 20%, 30%, 40%, and 50% response rates were obtained for 77%, 66%, 51%, and 35% of subjects, respectively.

Response Rates (Study R076477SCH3018: *Efficacy Analysis Set*)

Response rates	≥ 20% response				≥ 30% response				≥ 40% response				≥ 50% response			
	Yes		No		Yes		No		Yes		No		Yes		No	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Visit																
2: Day 2	13	4.4	281	95.6	2	0.7	292	99.3	0	0	294	100.0	0	0	294	100.0
3: Day 3	37	12.9	250	87.1	11	3.8	276	96.2	5	1.7	282	98.3	0	0	287	100.0
4: Day 4	86	29.9	202	70.1	34	11.8	254	88.2	20	6.9	268	93.1	8	2.8	280	97.2
5: Day 5	112	39.4	172	60.6	60	21.1	224	78.9	33	11.6	251	88.4	21	7.4	263	92.6
6: Day 7	159	55.6	127	44.4	109	38.1	177	61.9	56	19.6	230	80.4	32	11.2	254	88.8
7: Day 14	199	72.1	77	27.9	134	48.6	142	51.4	93	33.7	183	66.3	50	18.1	226	81.9
8: Day 28	203	79.9	51	20.1	170	66.9	84	33.1	122	48.0	132	52.0	76	29.9	178	70.1
9: Day 42	205	87.6	29	12.4	179	76.5	55	23.5	139	59.4	95	40.6	97	41.5	137	58.5
Endpoint	225	76.5	69	23.5	195	66.3	99	33.7	151	51.4	143	48.6	102	34.7	192	65.3

% improvement in total PANSS is calculated as the corrected response rate (=100% * (T-B) / (B-30) with T = follow up value and B = baseline value)
N = number of subjects with (no) response

- **Clinical Global Impression – Severity:**

Apart from 1 subject at Day 7 and endpoint, none of the subjects in this trial had a CGI-S score that placed them among the most extremely ill subjects. Judging from the CGI-S score, 74% of the subjects included in this trial were at least markedly ill at Day 1. After 6 weeks of treatment in the core treatment phase, at Day 42, the fraction of at least markedly ill subjects had decreased to 9%. Mean CGI-S score significantly decreased, indicating an improvement in overall severity of the subjects' psychotic condition, at all time points from baseline onwards ($p < 0.0001$). At Day 42, a mean (SD) statistically significant ($p < 0.0001$) decrease of 1.5 (0.9) from baseline was observed, corresponding to a CGI-S value of 2.4 (0.8).

Classification of Psychiatric Condition by CGI-S (Study R076477SCH3018: *Efficacy Analysis Set*)

CGI-S Class	Visit											
	1: Day 1		6: Day 7		7: Day 14		8: Day 28		9: Day 42		Endpoint	
	N	%	N	%	N	%	N	%	N	%	N	%
Among the most severely ill subjects	0	0	1	0.3	0	0	0	0	0	0	1	0.3
Severely ill	57	19.5	21	7.3	16	5.8	8	3.1	4	1.7	15	5.2
Markedly ill	160	54.6	100	34.8	59	21.4	42	16.5	18	7.7	42	14.5
Moderately ill	74	25.3	122	42.5	126	45.7	99	39.0	79	33.6	92	31.7
Mildly ill	2	0.7	42	14.6	72	26.1	92	36.2	114	48.5	118	40.7
Borderline mentally ill	0	0	1	0.3	3	1.1	12	4.7	18	7.7	20	6.9
Normal, not at all ill	0	0	0	0	0	0	1	0.4	2	0.9	2	0.7
Total	293	100.0	287	100.0	276	100.0	254	100.0	235	100.0	290	100.0

N = number of subjects in specific class

- **Personal and Social Performance Scale:**

At baseline, the percentage of subjects that were functioning so poorly that they required intensive supervision was 8%. At Day 42, after 6-weeks of treatment in the core treatment phase, this group of subjects had decreased to 1% of the entire population. At endpoint, the percentage of subjects in this category was 2%. At baseline, the majority of subjects (82%) had varying degrees of disability. At Day 42, this percentage had decreased to 62% (64% at endpoint). For the PSP class "mild degree of difficulty" the percentage of subjects at baseline was 10%, increasing up to 37% of the subjects at Day 42 and 33% at endpoint. Mean PSP score significantly increased, indicating an improvement in overall functionality, at all time points from baseline onwards ($p < 0.0001$). At Day 42, a mean (SD) increase of 16.1 (13.9) was observed versus baseline. At endpoint, the increase versus baseline was 13.7 (14.4).

Classification of Personal and Social Performance by PSP (Study R076477SCH3018: *Efficacy Analysis Set*)

PSP Class	Visit											
	1: Day 1		6: Day 7		7: Day 14		8: Day 28		9: Day 42		Endpoint	
	N	%	N	%	N	%	N	%	N	%	N	%
Functioning so poorly as to require intensive supervision	24	8.2	16	5.6	6	2.2	4	1.6	2	0.9	7	2.4
Varying degrees of disability	240	81.6	225	78.4	216	78.3	174	68.5	145	61.7	186	64.1
Mild degree of difficulty	30	10.2	46	16.0	54	19.6	76	29.9	88	37.4	97	33.4
Total	294	100.0	287	100.0	276	100.0	254	100.0	235	100.0	290	100.0

N = number of subjects in specific class

SAFETY RESULTS OF THE CORE PHASE:

Adverse Events

No subjects died during the core treatment phase of this study. Other SAEs (all of which were treatment-emergent) were reported for 8% of subjects.

Treatment-emergent AEs (TEAEs) rarely led to the permanent discontinuation of study medication (3% of subjects).

Subjects With Adverse Events/Reactions (Study R076477SCH3018: *Safety Analysis Set*)

n (%)	Total N = 294
One or more AE(s)	200 (68.0)
One or more TEAE(s)	199 (67.7)
One or more SAE(s)	23 (7.8)
One or more TESAE(s)	23 (7.8)
Deaths	0
One or more causally related AE(s)	91 (31.0)
One ore more causally related TEAE(s)	91 (31.0)
One or more TEAE(s) leading to permanent treatment discontinuation	9 (3.1)

N = total number of subjects; n = number of subjects with event

By body system, TEAEs were mostly related to psychiatric disorders (39%) and nervous system disorders (24%). By preferred term, the most common TEAEs were insomnia (24%), tachycardia (9%), headache (8%), extrapyramidal disorders (7%), and anxiety (5%).

The majority of TEAEs were mild (64%) or moderate (32%) in severity. Only 5% of all TEAEs were severe. The majority of TEAEs were considered not (50%) or doubtfully (20%) related to the study medication. Thirty percent of all TEAEs were considered at least possibly related to the study medication by the investigator (i.e., 18% were considered possibly related, 7% probably related, and 5% very likely related). The most common TEAEs with a causal relationship were extrapyramidal disorder (6%) and insomnia (5%).

EPS-related events were reported for 50 subjects (17%). The most common EPS-related symptoms were AEs in the category of parkinsonism (9%) or hyperkinesia (8%).

Glucose- and prolactin-related AEs were rarely reported (i.e., in 1% and 2% of subjects, respectively).

Treatment-Emergent Adverse Events/Reactions That Occurred In At Least 5% of Subjects During the Core Treatment Phase (Study R076477SCH3018: *Safety Analysis Set*)

Body System, Preferred term[a], n (%)	Total N= 294
Psychiatric disorders	**114 (38.8)**
Insomnia	69 (23.5)
Anxiety	16 (5.4)
Cardiac disorders	**32 (10.9)**
Tachycardia	26 (8.8)
Nervous system disorders	**69 (23.5)**
Extrapyramidal disorder	20 (6.8)
Headache	22 (7.5)

[a] Subjects with multiple occurrences of the same AE were counted only once for that particular preferred term or body system.

N = total number of subjects with data; n = number of subjects with event

Other Safety Parameters:

Body Weight

Body weight and BMI showed a statistically significant but not clinically relevant increase versus baseline at Day 42 (0.78 kg and 0.27 kg/m², respectively) and endpoint (0.63 kg and 0.22 kg/m², respectively) ($p < 0.0001$). Overall, 7% of the subjects showed a change in body weight ≥ 7% at endpoint (95% CI: 4.4%-11.0%).

EPS Assessment Scales

After 42 days of treatment, all 3 EPS assessments scales (AIMS, SAS, and BARS) showed slight improvement, although this was not statistically significant.

Vital Signs

Pulse, systolic blood pressure (SBP) and diastolic blood pressure (DBP) values showed small and rarely statistically significant changes over time at all time points.

Physical Examination

At baseline, 32% of all subjects in the safety analysis set were observed with 1 or more abnormalities during the physical examination. These abnormalities were mostly skin-related (8%), neurological (6%), or musculoskeletal (5%). After 6 weeks of treatment, physical examination results had changed in 8% of subjects. These changes were mostly related to neurological abnormalities.

SAFETY RESULTS OF THE CORE AND EXTENSION PHASE:

Data presented are safety results obtained throughout the entire trial for the extension population, i.e., 139 subjects who completed the core phase and who continued the extension phase of the trial.

Adverse Events

One subject died (acute methadone intoxication, considered not related to the trial medication by the investigator) during the extension phase of this study. Other SAEs (all of which were treatment-emergent) were reported for 22% of subjects.

Treatment-emergent AEs (TEAEs) led to the permanent discontinuation of study medication of the extension phase in 8% of the subjects.

Subjects With Adverse Events/Reactions (Study R076477SCH3018: *Safety Analysis Set*)

n (%)	Total N = 139
One or more AE(s)	97 (69.8)
One or more TEAE(s)	96 (69.1)
One or more SAE(s)	31 (22.3)
One or more TESAE(s)	31 (22.3)
Deaths	1
One or more causally related AE(s)	52 (37.4)
One or more causally related TEAE(s)	52 (37.4)
One or more TEAE(s) leading to permanent treatment discontinuation	11 (7.9)

N = total number of subjects; n = number of subjects with event

By body system, TEAEs were mostly related to psychiatric disorders (50%) and nervous system disorders (27%). By preferred term, the most common TEAEs were insomnia (22%), schizophrenia (15%), anxiety (10%), extrapyramidal disorder (9%), akathisia and tachycardia (7% each), hypertension (6%) and headache and psychotic disorder (5% each).

The majority of TEAEs were mild (59%) or moderate (36%) in severity. Only 6% of all TEAEs were severe. The majority of TEAEs were considered not (42%) or doubtfully (23%) related to the study medication. Thirty-four percent of all TEAEs were considered at least possibly related to the study medication by the investigator (i.e., 21% were considered possibly related, 9% probably related, and 5% very likely related).

Other Safety Parameters:

Body Weight

When evaluating the whole trial period, i.e., core phase followed by the extension phase, body weight and BMI of the extension population showed a statistically significant increase versus baseline (of the core phase) at endpoint: mean (SD) body weight had increased by 1.89 (6.38) kg ($p = 0.0002$), and mean (SD) BMI had increased by 0.66 (2.20) kg/m² ($p = 0.0003$). Overall, 20% of subjects showed a change in body weight ≥ 7% at endpoint (95% CI: 13.5%-27.6%).

CONCLUSION:

At endpoint of the core treatment phase, sixty-six percent of the subjects showed response to paliperidone ER (3-12 mg), defined as a decrease of at least 30% in PANSS total score.
In addition, treatment with paliperidone ER (flexible doses of 3-12 mg) resulted in statistically significant improvements in all efficacy parameters. As of the day after first paliperidone ER intake, the observed decrease of the mean total PANSS score was statistically significant, indicating a rapid onset of action.
No new or additional safety-related information emerged from this study.

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.