SYNOPSIS

Issue Date: 18 January 2011
Document No.: EDMS-ERI-19254103

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

Protocol No.: R076477SCH3017

Title of Study: An Open-label Prospective Trial to Explore the Tolerability, Safety and Efficacy of Flexibly Dosed Paliperidone ER in Subjects With Schizophrenia

EudraCT Number: 2006-004265-34

Coordinating/Principal Investigator: Not applicable.

Publication (Reference): None at the time of reporting

Study Period: from 24 April 2007 until 15 January 2009 (i.e., the latter is until last patient last visit of the 6-month paliperidone ER treatment and excluding the extension phase)

Phase of Development: 3b

Objectives:

PRIMARY
To explore the efficacy, based on total Positive and Negative Syndrome Scale (PANSS) score, of flexibly dosed paliperidone ER in subjects with schizophrenia previously unsuccessfully treated with other oral antipsychotics. For this purpose, 4 different groups of subjects were distinguished based upon the main reason for transition from their previous treatment to flexibly dosed paliperidone ER:

- lack of efficacy of the previous antipsychotic treatment;
- lack of tolerability or safety with the previous antipsychotic treatment;
- lack of compliance;
- other reasons.

For the group of subjects who transitioned for lack of efficacy, the primary objective was to investigate improved efficacy. For the other groups the primary objective was to investigate maintained efficacy.

SECONDARY
- To explore the tolerability and safety of flexibly dosed paliperidone ER in subjects with schizophrenia previously unsuccessfully treated with other oral antipsychotics;
- To explore the characteristics of response within different subgroups of the transition from previous oral antipsychotic medication to flexibly dosed paliperidone ER. This was done by assessing:
  - efficacy by means of PANSS;
  - proportion of subjects improving ≥ 20% in total PANSS from baseline to endpoint;
  - general measures of treatment success by means of the Clinical Global Impression-Severity score (CGI-S);
  - personal and social functioning by means of the Personal and Social Performance (PSP) scale;

- health status by means of the self-rated short form 36 (SF-36) Health Survey;
- subject satisfaction;
- evaluation of sleep quality and daytime drowsiness by means of a self-rated 11-point Evaluation Scale;
- side effect profiles by means of the Extrapyramidal Symptom Rating Scale (ESRS), body weight, vital signs, physical examination and adverse events (AEs).

Methods:

This was a non-randomized, open-label, single arm, multicenter, 6-month study aiming to explore the tolerability, safety and efficacy of flexibly dosed paliperidone ER in 2000 subjects with schizophrenia previously unsuccessfully treated with an oral antipsychotic medication. Subjects from any oral antipsychotic medication could be transitioned to an effective dose of paliperidone ER without the need for titration. Subjects could be either in- or outpatients. Subjects could be either cross-tapered or directly switched from their previous antipsychotic medication. A transition period of preferably a maximum of 4 weeks was allowed. Anticholinergic medication could be continued up to 4 weeks and was then to be tapered off at the discretion of the investigator. Throughout the study flexible dosing of paliperidone ER in a range of 3 to 12 mg/day could be used. Flexible dosing allowed investigators to individually adjust the dosage of each subject. The recommended dose of paliperidone ER was 6 mg once daily. Some subjects could benefit from higher or lower doses within the recommended range of 3 to 12 mg once daily. An interim analysis was performed on data of subjects who had completed the first 13 weeks of the study. Subjects who completed the 6-month study and liked to continue treatment with paliperidone ER were eligible to be enrolled in an extension phase until paliperidone ER was available. Subjects received, without cost, paliperidone ER. The starting dose of the extension phase was the same as at the end of the 6-month study period and could be changed throughout the extension period.

Antipsychotics and other psychotropic medication that were administered previous to trial start for other reasons than the disease itself, e.g. sleep induction or sedation could be continued during the trial, but the dose had to be kept stable. Other antipsychotics for the treatment of schizophrenia were not allowed. Benzodiazepines were allowed for rescue medication during the trial but not for a period longer than 10 consecutive days.
Benztropine mesylate or biperidene up to 4 mg/day or trihexyphenidyl up to 10 mg/day could be used for the treatment of EPS. The investigator had to reevaluate the need for anticholinergic medication on an ongoing basis.
The sponsor had to be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies were administered.

No data monitoring committee was engaged in this study.

A planned interim analysis was performed based on the first 13 weeks of the core-treatment phase of the first 81 subjects enrolled because of lack of efficacy and of the first 124 subjects enrolled because of lack of tolerability of their previous antipsychotic medication who were included in the intent-to-treat (ITT) analysis.

If there was a substantial number of protocol violators (e.g., > 10%), an additional per-protocol analysis could be performed. As 326 (18.0%) subjects had a major protocol deviation, a per-protocol analysis was performed.

Number of Subjects (planned and analyzed):

A total of approximately 2000 subjects were planned for the core treatment phase of this study. The number of subjects randomized, randomized and treated, and included in the several analysis sets, are presented in the table below.

Subject Disposition and Completion/Withdrawal Information
(R076477SCH3017 Study)

N	Lack of Efficacy	Lack of Tolerability	Lack of Compliance	Other	Total
Screened	-	-	-	-	1848
Interim Analysis (Lack of Efficacy Subgroup)					
ITT	81	-	-	-	-
Interim Analysis (Lack of Tolerability Subgroup)					
ITT	-	124	-	-	-
Full Analysis					
ITT (All subjects)[a]	1025	490	165	132	1812
Efficacy analysis[b]	998	477	155	128	1758
Safety analysis[c]	1025	490	165	131	1811
Per-protocol analysis[d]	849	394	133	110	1486

N = number of subjects with data

[a] The ITT analysis set consisted of all subjects who received paliperidone ER at least once and was used in the analysis of the demographic and baseline characteristic data.

[b] The ITT analysis set for efficacy consisted of all subjects who received paliperidone ER at least once and provided ≥ 1 postbaseline efficacy measurement.

[c] The ITT analysis set for safety consisted of all subjects who received paliperidone ER at least once and provided any postbaseline information.

[d] The per-protocol analysis set excluded subjects from the ITT analysis set who had a major protocol deviation.

Diagnosis and Main Selection Criteria:

Adult male and female subjects (≥ 18 years) who were able to read and met the DSM-IV criteria for schizophrenia were eligible for this study. Subjects were previously non-acute, i.e. on the same antipsychotic medication used for the treatment of schizophrenia and CGI-S change ≤ 1 in the past 4 weeks before enrollment. Subjects were given an adequate dose of an appropriate oral antipsychotic for an adequate period of time prior to enrollment, but previous treatment was considered unsuccessful due to one or more of the following reasons: lack of efficacy, lack of tolerability or safety, lack of compliance and/or other reasons to switch to another antipsychotic medication.

Subjects who were on clozapine, any conventional depot neuroleptic or Risperdal CONSTA during the last 3 months were excluded as well as subjects with a serious unstable medical condition, a history or current symptoms of tardive dyskinesia and a history of neuroleptic malignant syndrome.

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

There were 4 dosage levels of paliperidone ER (Invega®): 3, 6, 9, and 12 mg/day. In general, the recommended paliperidone ER dose was 6 mg once daily. Some subjects could benefit from higher or lower doses in the recommended range of 3 to 12 mg once daily. Throughout the study flexible dosing in a range of 3 to 12 mg/day could be used. Paliperidone ER 3-mg, 6-mg and 12-mg tablets were used.

Study Medication	Batch Number	Expiry Date
Paliperidone ER 3-mg and 6 mg tablet kits	0620766	30 June 2008
	0617714	30 June 2008
	0620769	30 June 2008
	0607491	30 June 2008
	0627123	31 October 2008
	0707704	31 October 2008
	0716337	31 October 2008
	0706412	30 November 2008
	0729774	31 October 2010
	0729777	31 July 2010
	0722792	31 July 2010
Paliperidone ER 12-mg tablet kits	0602596	29 February 2008*
	7AG1026-X	31 January 2009

* expiry date extended with 12 months

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

Duration of Treatment: 6 months

Criteria for Evaluation:

EFFICACY EVALUATIONS/CRITERIA:

All subjects who received paliperidone ER at least once and provide ≥ 1 postbaseline efficacy measurement were included in efficacy data analyses.

Analyses included the following:

- Efficacy as measured by the change from baseline in PANSS total score;
- Change in PANSS positive and negative subscores and Marder factors including efficacy on anxiety and depression as measured by the PANSS anxiety/depression factor;
- Global improvement, which was based on the change from baseline in CGI-S score;
- Personal and social functioning as measured by the change in PSP;
- Health status as measured by the change from baseline in SF-36;
- Subject Satisfaction using a 5-point evaluation scale;
- Effects on sleep-related endpoints, e.g. quality of sleep and daytime drowsiness as measured by an eleven-item categorical scale.

SAFETY EVALUATIONS:

A physical examination was completed at screening, at Week 26 and at study end or at the time of discontinuation. A urine pregnancy test was performed in all females of childbearing age at screening, at Week 26, at end of the extension phase (if applicable) or at early discontinuation. Vital signs were assessed at each scheduled visit and during any unscheduled visits. The ESRS was completed at each scheduled visit and at early discontinuation. Body weight was measured at screening, at Weeks 13 and 26, at the end of the extension phase or at early discontinuation. Subjects were instructed to report AEs as they emerged; AEs were assessed at each study visit after informed consent had been obtained.

Statistical Methods: Descriptive statistics, intent-to-treat analysis, frequency distributions, Wilcoxon-signed-rank test

RESULTS:

This Clinical Study Report describes the results of the 6-month core treatment phase. Results of the extension phase will be described in a separate report. This extension phase was still ongoing at the moment of finalization of this Clinical Study Report.

Based upon the main reason for switching from their previous treatment to paliperidone ER, 4 different groups of subjects were distinguished:

- lack of efficacy of the previous antipsychotic treatment;
- lack of tolerability or safety with the previous antipsychotic treatment;
- lack of compliance to the previous antipsychotic treatment;
- other reasons.

Throughout this section, these subgroups will be referred to as the lack of efficacy, lack of tolerability, lack of compliance, and other reason subgroups, respectively.

A total of 1812 subjects were enrolled in this study, of which the majority were included in the lack of efficacy subgroup (1025 [56.6%] subjects). The lack of tolerability subgroup consisted of 490 (27.0%) subjects, the lack of compliance subgroup of 165 (9.1%) subjects and the other reason subgroup of 132 (7.3%) subjects.

Most subjects switched to paliperidone ER from risperidone (694 [38.3%] subjects), olanzapine (396 [21.9%] subjects) or haloperidol (191 [10.5%] subjects).

Overall, 1283 out of 1812 subjects (70.8%) completed the trial. Five hundred and twenty-nine (29.2%) subjects receiving paliperidone ER discontinued the study prematurely. The main reasons for premature discontinuation were withdrawal of consent (160 subjects, 8.8%), followed by lack of efficacy (91 subjects, 5.0%), an AE (91 subjects, 5.0%), and a combination of an AE and lack of efficacy (73 subjects, 4.0%). The number of subjects who discontinued study medication was similar between the 4 subgroups based upon the main reason for switching from previous antipsychotic medication to paliperidone ER.

Subject Disposition and Completion/Withdrawal Information
(R076477SCH3017 Study: ITT All Subjects)

	Main Reason for Switching to Paliperidone ER				
	Lack of Efficacy N = 1025	Lack of Tolerability N = 490	Lack of Compliance N = 165	Other N = 132	Total N = 1812
Completed, n (%)	730 (71.2)	334 (68.2)	121 (73.3)	98 (74.2)	1283 (70.8)
Withdrawn, n (%)					
Withdrawal of consent	89 (8.7)	45 (9.2)	14 (8.5)	12 (9.1)	160 (8.8)
Lack of efficacy	60 (5.9)	22 (4.5)	6 (3.6)	3 (2.3)	91 (5.0)
AE	41 (4.0)	40 (8.2)	4 (2.4)	6 (4.5)	91 (5.0)
AE and lack of efficacy	44 (4.3)	24 (4.9)	1 (0.6)	4 (3.0)	73 (4.0)
Other	19 (1.9)	10 (2.0)	9 (5.5)	5 (3.8)	43 (2.4)
Study medication non-compliance	17 (1.7)	9 (1.8)	6 (3.6)	3 (2.3)	35 (1.9)
Lost to follow-up	22 (2.1)	6 (1.2)	4 (2.4)	1 (0.8)	33 (1.8)
Death	3 (0.3)	0	0	0	3 (0.2)

N = number of subjects with data, n = number of subjects with that observation

The majority of the subjects were male (1086 [59.9%] subjects). Mean (SD) age was 40.1 (12.6) years. Demographic and baseline characteristics were comparable for the subjects in the 4 different subgroups based upon main reason for switching to paliperidone ER (see table below).

The majority of subjects had paranoid schizophrenia (1373 [75.8%] subjects), followed by the undifferentiated type (213 [11.8%] subjects) and the residual type (123 [6.8%] subjects). The course of schizophrenia was mainly episodic with residual symptoms (888 [49.0%] subjects), continuous (522 [28.8%] subjects) or episodic without residual symptoms (255 [14.1%] subjects).

The most frequently (> 10% of all subjects) used antipsychotics at baseline were risperidone (681 [37.6%] subjects), olanzapine (379 [20.9%] subjects) and haloperidol (184 [10.2%] subjects).

Results of the Per-Protocol population were similar.

Demographic and baseline characteristics
(R076477SCH3017 Study: ITT Analysis Set)

	Main Reason for Switching to Paliperidone ER				
Parameter	Lack of Efficacy	Lack of Tolerability	Lack of Compliance	Other	Total
Gender, n (%)					
N	1025	490	165	132	1812
Female	404 (39.4)	206 (42.0)	69 (41.8)	47 (35.6)	726 (40.1)
Male	621 (60.6)	284 (58.0)	96 (58.2)	85 (64.4)	1086 (59.9)
Age (years)					
N	1025	490	165	132	1812
Mean (SD)	40.2 (12.8)	39.5 (12.3)	39.9 (12.7)	41.3 (11.7)	40.1 (12.6)
Median	39	39	38	43	39
Range	17; 93	18; 74	18; 70	20; 78	17; 93
Weight (kg)					
N	1024	489	165	130	1808
Mean (SD)	80.3 (18.1)	84.1 (17.9)	78.3 (15.9)	78.5 (16.8)	81.0 (17.9)
Median	79	83	76	74	79
Range	36; 160	45; 172	41; 128	50; 136	36; 172
Height (cm)					
N	1022	488	165	130	1805
Mean (SD)	171.1 (10.1)	172.1 (9.9)	170.9 (9.3)	171.9 (9.5)	171.4 (9.9)
Median	171	172	171	171	171
Range	129; 214	144; 198	148; 198	151; 196	129; 214
BMI (kg/m²)					
N	1021	488	165	130	1804
Mean (SD)	27.40 (5.6)	28.36 (5.5)	26.82 (5.3)	26.53 (5.2)	27.54 (5.5)
Median	26.5	27.5	25.6	25.3	26.7
Range	15.7; 51.9	17.6; 58.8	17.6; 51.7	17.9; 54.3	15.7; 58.8
Pulse rate (bpm)					
N	1021	489	165	130	1805
Mean (SD)	79.1 (10.8)	79.0 (11.6)	79.4 (12.0)	77.8 (10.2)	79.0 (11.1)
Median	78	80	76	76	78
Range	46; 135	48; 120	56; 120	54; 108	46; 135
Systolic blood pressure (mmHg)					
N	1021	489	165	130	1805
Mean (SD)	123.6 (13.8)	125.6 (13.8)	125.6 (15.0)	123.6 (14.2)	124.3 (13.9)
Median	120	124	122	120	121
Range	85; 200	80; 178	97; 188	95; 178	80; 200
Diastolic blood pressure (mmHg)					
N	1021	489	165	130	1805
Mean (SD)	78.2 (9.1)	80.2 (9.9)	78.7 (9.3)	77.8 (8.8)	78.8 (9.3)
Median	80	80	80	80	80
Range	50; 115	40; 120	57; 118	60; 106	40; 120

N = number of subjects with data; n = number of subjects with that observation

Baseline Disease Characteristics: Schizophrenia
(R076477SCH3017 Study: ITT Analysis Set)

	Main Reason for Switching to Paliperidone ER				
Parameter	Lack of Efficacy	Lack of Tolerability	Lack of Compliance	Other	Total
Age[a] at first onset of psychotic symptoms					
N	944	466	157	123	1690
Mean (SD)	26.9 (9.6)	27.6 (9.4)	27.4 (9.0)	28.3 (9.8)	27.3 (9.5)
Median	24	25	25	26	25
Range	5; 70	12; 74	14; 55	14; 54	5; 74
Duration[b] since first onset of psychotic symptoms					
N	944	466	157	123	1690
Mean (SD)	13.0 (10.4)	12.1 (10.1)	12.5 (10.8)	13.4 (9.5)	12.7 (10.3)
Median	10	9	10	11	10
Range	0; 55	0; 48	0; 52	1; 41	0; 55
Age[a] at first antipsychotic treatment					
N	960	472	156	120	1708
Mean (SD)	28.7 (10.1)	28.7 (9.4)	28.5 (9.4)	29.5 (10.2)	28.7 (9.8)
Median	26	26	27	28	26
Range	7; 82	12; 74	14; 57	14; 56	7; 82
Duration[b] since first antipsychotic treatment					
N	960	472	156	120	1708
Mean (SD)	11.3 (9.9)	11.0 (10.0)	11.1 (10.4)	11.7 (9.6)	11.2 (10.0)
Median	9	8	8	9	8
Range	0; 49	0; 48	0; 52	0; 41	0;52
Age[a] at first diagnosis of schizophrenia					
N	968	475	153	120	1716
Mean (SD)	29.8 (10.4)	30.0 (9.9)	30.1 (10.3)	30.9 (10.4)	30.0 (10.2)
Median	27	28	28	30	28
Range	7; 82	12; 75	14; 63	14; 56	7; 82
Duration[b] since first diagnosis of schizophrenia					
N	968	475	153	120	1716
Mean (SD)	10.3 (9.9)	9.6 (9.6)	9.4 (9.5)	10.4 (8.8)	10.1 (9.7)
Median	8	6	6	8	7
Range	0; 49	0; 48	0; 42	0; 40	0; 49
Type of schizophrenia, n (%)					
N	1025	490	164	132	1811
Paranoid	761 (74.2)	386 (78.8)	125 (76.2)	101 (76.5)	1373 (75.8)
Undifferentiated	128 (12.5)	54 (11.0)	15 (9.1)	16 (12.1)	213 (11.8)
Residual	70 (6.8)	33 (6.7)	10 (6.1)	10 (7.6)	123 (6.8)
Disorganized	57 (5.6)	15 (3.1)	11 (6.7)	5 (3.8)	88 (4.9)
Catatonic	3 (0.3)	2 (0.4)	1 (0.6)	0	6 (0.3)
Other[c]	6 (0.6)	0	2 (1.2)	0	8 (0.4)

[a] Age was based on the difference between year of birth and year of onset, meaning that age could actually be almost 1 year more as day and month were not taken into consideration.

[b] Duration was based on the difference between 2 years, meaning that a duration of 0 years could actually be almost 1 year as day and month were not taken into consideration.

[c] Other included catatonic, pseudoneurotic, bipolar disorder, coenesthetic, coenestopatic, schizophrenia simplex.

N = number of subjects with data; n = number of subjects with that observation

Baseline Disease Characteristics: Schizophrenia, Cont'd
(R076477SCH3017 Study: ITT Analysis Set)

	Main Reason for Switching to Paliperidone ER				
	Lack of Efficacy	Lack of Tolerability	Lack of Compliance	Other	Total
Course of schizophrenia, n (%)					
N	1025	490	164	132	1811
Episodic with residual symptoms	512 (50.0)	238 (48.6)	81 (49.4)	57 (43.2)	888 (49.0)
Continuous	352 (34.3)	89 (18.2)	36 (22.0)	45 (34.1)	522 (28.8)
Episodic without residual symptoms	100 (9.8)	101 (20.6)	33 (20.1)	21 (15.9)	255 (14.1)
Single episode in partial remission	39 (3.8)	32 (6.5)	7 (4.3)	2 (1.5)	80 (4.4)
Single episode in full remission	4 (0.4)	7 (1.4)	4 (2.4)	1 (0.8)	16 (0.9)
Other or unspecified pattern	11 (1.1)	15 (3.1)	3 (1.8)	6 (4.5)	35 (1.9)
Not known/ not applicable	7 (0.7)	8 (1.6)	0	0	15 (0.8)

N = number of subjects with data; n = number of subjects with that observation

Data on hospitalization and the age and duration of the first onset of psychotic symptoms, first antipsychotic treatment and first diagnosis of schizophrenia is provided in the following table.

Baseline Disease Characteristics: Hospitalization
(R076477SCH3017 Study: ITT Analysis Set)

	Main Reason for Switching to Paliperidone ER				
	Lack of Efficacy	Lack of Tolerability	Lack of Compliance	Other	Total
Age[a] at first psychiatric hospitalization					
N	868	422	134	102	1526
Mean (SD)	29.3 (10.0)	29.3 (9.7)	29.5 (10.2)	29.6 (10.0)	29.4 (10.0)
Median	27	27	27	28	27
Range	7; 82	12; 75	14; 59	14; 57	7; 82
Duration[b] since first psychiatric hospitalization					
N	868	422	134	102	1526
Mean (SD)	11.7 (10.6)	10.9 (10.1)	11.8 (11.0)	12.7 (10.2)	11.6 (10.5)
Median	9	8	8	10	9
Range	0; 52	0; 48	0; 50	0; 41	0; 52
Subjects hospitalized at least once ever					
Number of subjects					
N	1025	490	165	132	1812
n (%)	895 (87.3)	432 (88.2)	138 (83.6)	106 (80.3)	1571 (86.7)
Number hospitalizations					
N	809	402	125	97	1433
Mean (SD)	4.6 (5.9)	4.0 (6.0)	4.7 (6.1)	4.6 (5.1)	4.5 (5.9)
Median	3	2	2	3	3
Range	0; 52	0; 80	0; 38	0; 37	0; 80
Subjects hospitalized at least once in the previous 12 months					
Number hospitalizations					
N	271	127	49	29	476
Mean (SD)	1.4 (1.0)	1.3 (0.6)	1.3 (0.5)	1.2 (0.4)	1.4 (0.9)
Median	1	1	1	1	1
Range	1; 13	1; 5	1; 3	1; 2	1; 13
Duration (days)					
N	271	127	49	28[c]	475
Mean (SD)	63.4 (64.8)	52.8 (49.9)	59.2 (62.0)	37.2 (30.2)	58.6 (59.5)
Median	41	41	38	23	39
Range	2; 360	1; 294	9; 292	8; 114	1; 360
Subjects hospitalized at study start					
N	1025	490	165	132	1812
n (%)	236 (23.0)	50 (10.2)	41 (24.8)	13 (9.8)	340 (18.8)

[a] Age was based on the difference between year of birth and year of onset, meaning that age could actually be almost 1 year more as day and month were not taken into consideration.
[b] Duration was based on the difference between 2 years, meaning that a duration of 0 years could actually be almost 1 year as day and month were not taken into consideration.
[c] Subject who was hospitalized during the past 12 months, but with unknown duration.
N = number of subjects with data; n = number of subjects with that observation

EFFICACY RESULTS:

Primary Efficacy Analysis

For subjects who transitioned for the main reason of lack of efficacy of previous antipsychotic medication, the percentage of subjects with at least 20% improvement in total PANSS from baseline to endpoint was the primary efficacy parameter. For subjects who transitioned for the main reason of lack of tolerability, lack of compliance or other reasons, the change from baseline to endpoint in the total PANSS score was the primary efficacy parameter, which was used to test non-inferiority in efficacy between paliperidone and previous antipsychotic medication by means of the Schuirmann's test. A difference of 5 points in change from baseline to endpoint in total PANSS score is considered to be a minimum clinically meaningful difference.

In the lack of efficacy subgroup, 612 (61.3%) had at least 20% improvement in total PANSS score from baseline to endpoint after treatment with paliperidone ER. The lower and upper limits of the 95% CI were 58.2% and 64.4%, respectively.

In the lack of tolerability, lack of compliance and other reason subgroups, Schuirmann's one-sided test rejected the null hypotheses of non-inferiority so that equivalence to within the specified equivalence bounds could be claimed for all 3 subgroups of subjects based on the main reason for switching. Moreover, schizophrenia symptoms were statistically significantly and clinically meaningfully improved in the lack of tolerability, lack of compliance and other reason subgroups, with the largest improvement in the lack of compliance subgroup.

Primary Efficacy Parameter: Total PANSS
(R076477SCH3017 Study: ITT Analysis Set for Efficacy)

	Main Reason for Switching to Paliperidone ER			
	Lack of Efficacy	Lack of Tolerability	Lack of Compliance	Other
Primary efficacy parameter for subgroup lack of efficacy				
Responders with ≥ 20% improvement in total PANSS from baseline to endpoint				
N	998	-	-	-
n (%)	612 (61.3)	-	-	-
95% CI	58.2-64.4	-	-	-
Primary efficacy parameter for subgroups lack of tolerability, lack of compliance and other				
N	-	475	155	128
Total PANSS at baseline				
Mean (SD)	-	68.3 (18.0)	78.9 (21.7)	74.1 (21.8)
Median	-	67	76	73
Range	-	31; 125	37; 139	30; 155
Total PANSS at endpoint				
Mean (SD)	-	59.9 (19.8)	60.5 (22.3)	64.5 (22.5)
Median	-	56	55	63
Range	-	30; 146	30; 140	30; 149
Change from baseline at endpoint in total PANSS				
Mean (SD)	-	-8.4 (19.2)	-18.4 (21.2)	-9.5 (17.3)
Median	-	-8	-17	-9
Range	-	-64; 75	-86; 50	-50; 67
p-value [a]	-	< 0.0001	< 0.0001	< 0.0001

N = number of subjects with data, n = number of subjects with that observation
[a] Non-inferiority testing using Schuirmann's one-sided test

Secondary Efficacy Analysis

Positive and Negative Syndrome Scale (PANSS)

The total PANSS scores showed a consistent and statistically significant improvement of symptoms over the 6-month treatment period in all subgroups (all $p < 0.0001$). The largest improvement was observed in the lack of efficacy and lack of compliance subgroups. In all subgroups, the positive, negative and general psychopathology subscales decreased consistently over the 6-month treatment period with statistically significant improvements from baseline at any postbaseline assessment and endpoint (all $p < 0.0001$). Within each subscale, no obvious differences between subgroups were observed in the changes from baseline to endpoint.

At endpoint, 1059 (60.3%) subjects had a response rate of at least 20%, 831 (47.3%) subjects had one of at least 30% and 635 (36.2%) and 472 (26.9%) subjects had a response rate of at least 40 and 50%, respectively. Within each category of total PANSS response rate, the lack of compliance subgroup showed the highest response rates; the other 3 subgroups had comparable responses.

Clinical Global Impression – Severity (CGI-S)

Over the 6-month treatment period, the CGI-S scores showed consistent improvement in the total study population as well as all subgroups. Statistically significant improvements from baseline to all time points and endpoint were observed in the total study population and in all subgroups (all $p < 0.0001$), except at Week 4 for subjects who had another main reason for switching to paliperidone ER than lack of efficacy, tolerability or compliance of previous antipsychotic medication ($p = 0.2885$). Observations were similar between subgroups.

Personal and Social Performance Scale (PSP)

The PSP total scores showed a consistent improvement over the 6-month treatment period in the total study population as well as all subgroups. Improvements from baseline to all time points and endpoint were statistically significant in the total study population and in all subgroups (all $p \leq 0.0002$). A somewhat larger improvement was observed in the lack of efficacy and lack of compliance subgroups compared to the lack of tolerability or other reason subgroups.

Within the subgroups and the total study population, subjects showed a somewhat larger improvement from baseline to endpoint in the domains socially useful activities and personal and social relationships compared to self-care and disturbing and aggressive behavior.

Subject Satisfaction

At endpoint, subject satisfaction with paliperidone ER treatment was good to very good in 1105 (67.3%) subjects, moderate in 292 (17.8%) subjects and poor to very poor in 246 (15.0%) subjects.

Sleep and Daytime Drowsiness Evaluation Scale

In the total study population, quality of sleep over the past 7 days was statistically significantly improved at endpoint compared to baseline ($p < 0.0001$). Within the subgroups, statistically significant improvements from baseline to endpoint were only observed in the lack of efficacy and the lack of compliance subgroups.

The drowsiness frequency over the past 7 days showed statistically significant improvement in the total study population and in all subgroups at all time points and endpoint (all $p \leq 0.0034$).

Self-Rated Health Status Survey SF-36

A statistically significant improvement in the total study population's physical and mental status was observed from baseline to endpoint ($p < 0.0001$). Statistically significant improvements in physical and mental status were also observed within all subgroups from baseline to endpoint (all $p \leq 0.0225$), except in the other reason subgroup for the physical component ($p = 0.0861$). Observations were similar between subgroups.

Efficacy results of the Per-Protocol population were generally similar.

SAFETY RESULTS:

Adverse Events

A summary of the treatment-emergent AEs (TEAEs) during the 6-month treatment period is presented in the table below.

Summary of Treatment-Emergent Adverse Events
(R076477SCH3017 Study: ITT Analysis Set for Safety)

	Main Reason for Switching to Paliperidone ER				
	Lack of Efficacy	Lack of Tolerability	Lack of Compliance	Other	Total
Subjects (n [%]) with	N = 1025	N = 490	N = 165	N = 131	N = 1811
at least one TEAE	552 (53.9)	319 (65.1)	69 (41.8)	67 (51.1)	1007 (55.6)
at least one treatment-emergent SAE	89 (8.7)	52 (10.6)	10 (6.1)	9 (6.9)	160 (8.8)
at least one TEAE that was considered possibly, probably, or very likely related to study medication by the investigator	354 (34.5)	206 (42.0)	42 (25.5)	39 (29.8)	641 (35.4)
TEAEs					
that were severe					
N'	1377	859	189	178	2603
(n'[%])	117 (8.5)	103 (12.0)	15 (7.9)	9 (5.1)	244 (9.4)
led to permanent discontinuation of the study medication					
N'	1379	859	189	178	2605
(n'[%])	130 (9.4)	94 (10.9)	10 (5.3)	17 (9.6)	251 (9.6)
for which concomitant therapy was started					
N'	1377	859	189	178	2603
(n'[%])	596 (43.3)	330 (38.4)	74 (39.2)	64 (36.0)	1064 (40.9)

N = number of subjects with data; n = number of subjects with one or more event;
N' = total number of TEAEs in that subgroup; n' = number of TEAEs with that characteristic

Overall, 1007 (55.6%) subjects had at least one TEAE during the core phase of this study, of which 552 (53.9%) in the lack of efficacy subgroup, 319 (65.1%) in the lack of tolerability subgroup, 69 (41.8%) in the lack of compliance subgroup, and 67 (51.1%) in the other reason subgroup.

Three (0.2%) subjects died during the core phase of the study, who were all included in the lack of efficacy subgroup. Treatment-emergent SAEs were reported in 160 (8.8%) subjects. Of all TEAEs, 251 (9.6%) led to permanent discontinuation of study medication.

Treatment-emergent adverse events reported in ≥ 2% of all subjects are presented in the following table. The most frequently reported TEAEs (≥ 5% of all subjects) were insomnia (167 [9.2%] subjects) and anxiety (130 [7.2%] subjects).

Treatment-Emergent Adverse Events Reported in ≥ 2% of all Subjects by Decreasing Total Number of Subjects
(R076477SCH3017 Study: ITT Analysis Set for Safety)

	Main Reason for Switching to Paliperidone ER				
Body Class, Preferred term, n (%)	Lack of Efficacy N = 1025	Lack of Tolerability N = 490	Lack of Compliance N = 165	Other N = 131	Total N = 1811
Subjects with at least one TEAE	*552 (53.9)*	*319 (65.1)*	*69 (41.8)*	*67 (51.1)*	*1007 (55.6)*
Psychiatric Disorders	263 (25.7)	181 (36.9)	34 (20.6)	37 (28.2)	515 (28.4)
Insomnia	88 (8.6)	58 (11.8)	11 (6.7)	10 (7.6)	167 (9.2)
Anxiety	76 (7.4)	37 (7.6)	9 (5.5)	8 (6.1)	130 (7.2)
Depression	39 (3.8)	22 (4.5)	8 (4.8)	1 (0.8)	70 (3.9)
Sleep disorder	26 (2.5)	20 (4.1)	4 (2.4)	5 (3.8)	55 (3.0)
Psychotic disorder	21 (2.0)	16 (3.3)	5 (3.0)	3 (2.3)	45 (2.5)
Agitation	25 (2.4)	13 (2.7)	1 (0.6)	1 (0.8)	40 (2.2)
Nervous System Disorders	232 (22.6)	120 (24.5)	25 (15.2)	24 (18.3)	401 (22.1)
Somnolence	43 (4.2)	22 (4.5)	6 (3.6)	5 (3.8)	76 (4.2)
Extrapyramidal disorder	42 (4.1)	16 (3.3)	4 (2.4)	3 (2.3)	65 (3.6)
Headache	31 (3.0)	25 (5.1)	3 (1.8)	6 (4.6)	65 (3.6)
Akathisia	38 (3.7)	12 (2.4)	4 (2.4)	2 (1.5)	56 (3.1)
Tremor	25 (2.4)	7 (1.4)	5 (3.0)	3 (2.3)	40 (2.2)
Gastrointestinal Disorders	89 (8.7)	63 (12.9)	10 (6.1)	12 (9.2)	174 (9.6)
Nausea	25 (2.4)	20 (4.1)	2 (1.2)	3 (2.3)	50 (2.8)
Infections and Infestations	66 (6.4)	43 (8.8)	8 (4.8)	11 (8.4)	128 (7.1)
Nasopharyngitis	17 (1.7)	15 (3.1)	3 (1.8)	4 (3.1)	39 (2.2)
Investigations	57 (5.6)	32 (6.5)	10 (6.1)	14 (10.7)	113 (6.2)
Weight increased	33 (3.2)	19 (3.9)	5 (3.0)	8 (6.1)	65 (3.6)
General Disorders and Administration Site Conditions	53 (5.2)	33 (6.7)	9 (5.5)	10 (7.6)	105 (5.8)
Fatigue	28 (2.7)	17 (3.5)	7 (4.2)	4 (3.1)	56 (3.1)
Vascular Disorders	25 (2.4)	8 (1.6)	3 (1.8)	1 (0.8)	37 (2.0)
Hypertension	16 (1.6)	4 (0.8)	2 (1.2)	1 (0.8)	23 (1.3)

N = number of subjects with data; n = number of subjects with one or more event

Vital Signs

Changes from baseline to endpoint in pulse rate, SBP and DBP were small and not statistically significant in any subgroup, except in the lack of compliance subgroup for pulse rate ($p = 0.0470$) and in the lack of tolerability subgroup for DBP ($p = 0.0006$). None of the changes from baseline were considered clinically meaningful. The most frequently reported vital signs-related TEAE was hypertension (23 [1.3%] subjects).

Bode Weight and BMI

At baseline and endpoint, the mean (SD) body weight in the total study population was 81.11 (17.80) and 81.41 (17.34) kg, respectively. Changes from baseline in body weight were small at any time point and endpoint. Body weight was statistically significantly increased in the total study population and in all subgroups at endpoint compared to baseline (all $p \leq 0.0023$), except in the lack of tolerability subgroup where a decrease in weight was observed (not statistically significant). However, these changes from baseline were not considered clinically meaningful. Increased weight was reported as a TEAE in 65 (3.6%) subjects and decreased weight in 17 (0.9%) subjects.

Results of BMI changes during the core phase were similar to body weight. At baseline and endpoint, the mean (SD) BMI in the total study population was 27.58 (5.55) and 27.70 (5.46) kg/m², respectively. Changes from baseline in BMI were small at any time point and endpoint. The BMI was statistically significantly increased in the total study population and in all subgroups at endpoint compared to baseline

(all $p \leq 0.0014$), except in the lack of tolerability subgroup where a decrease in BMI was observed (not statistically significant). However, these changes from baseline were not considered clinically meaningful.

Extrapyramidal Symptom Rating Scale (ESRS)

The total ESRS scores of the total study population showed a consistent and statistically significant improvement of extrapyramidal symptoms over the 6 month treatment period (all $p < 0.0001$). Within the subgroups, the total ESRS score was statistically significantly decreased at all time points and endpoint compared to baseline ($p \leq 0.0352$). At baseline, mean (SD) total ESRS scores were larger in the in the lack of efficacy (3.5 [5.7]) and lack of tolerability (4.6 [6.7]) subgroups compared to the lack of compliance (1.6 [4.4]) and other reason (1.8 [3.1]) subgroups. At endpoint versus baseline, improvement was somewhat larger in the lack of efficacy (mean [SD] change: -1.2 [4.2]) and lack of tolerability (-2.3 [5.3]) subgroups compared to the lack of compliance (-0.5 [3.4]) and other reason (-0.5 [2.3]) subgroups.

Hospitalization

In the total study population, 339 (18.7%) subjects were hospitalized at baseline. Within the subgroups, a higher percentage subjects was hospitalized at baseline in the lack of compliance (41 [24.8%] subjects) and lack of efficacy (236 [23.0%] subjects) subgroups compared to the lack of tolerability (50 [10.2%] subjects) and other reason (12 [9.2%] subjects) subgroups. Overall, 128 (7.1%) subjects were hospitalized from baseline to their endpoint in the study.
Hospitalization data of hospitalizations starting during the 6 months prestudy and of hospitalizations starting during the 6-month core phase (i.e., new hospitalizations) were analyzed. For hospitalizations starting prestudy and continuing during the study all hospital days were counted prestudy.
In the total study population, the number of hospital stays per subject per month statistically significantly decreased ($p < 0.0001$) from prestudy to during the study which was accompanied by a statistically significant ($p < 0.0001$) decrease in hospital days per subject per month.
Within the subgroups, the largest mean (SD) decrease in hospital stays from prestudy to during the study per subject per month was observed in the lack of compliance (-0.038 [0.154]) and lack of efficacy (-0.018 [0.202]) subgroups, which was statistically significant ($p < 0.0001$) in both subgroups. No clinically meaningful changes were observed in the lack of tolerability and other reason subgroups.
All subgroups showed a statistically significant ($p \leq 0.0073$) decrease (i.e., improvement) in hospital days per subject per month from prestudy to during the study. A larger mean (SD) decrease in hospital days from prestudy to during the study per subject per month was observed in the lack of compliance (-2.504 [5.288]) and lack of efficacy (-2.068 [5.343]) subgroups than in the lack of tolerability (-1.292 [4.277]) and other reason (-0.892 [5.063]) subgroups.
Similar trends were observed for the data of the subjects who were hospitalized prior to or during the study.

Physical Examination

Overall, 325 (19.8%) subjects had an abnormal observation upon physical examination at endpoint. The percentage of subjects with an abnormal observation upon physical examination at endpoint was lower in the lack of compliance subgroup (11.9% of all subjects) compared to lack of efficacy (18.8%), lack of tolerability (22.9%) and the other (25.0%) subgroups.

Anti-Parkinson Medication

The total percentage of subjects taking anti-parkinson medication decreased during the 6 month treatment phase: from 16.2% (294/1811) subjects at baseline to 12.5% (221/1763) subjects at endpoint. A similar decease was observed in all subgroups, except in the other reason subgroup where intake of anti-parkinson medication remained remained at a low level of 5.3 to 7.0% of subjects during the core phase.

Safety results of the Per-Protocol population were generally similar.

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

CONCLUSION:

Subjects who switched to paliperidone ER for the main reason of lack of efficacy of their previous antipsychotic medication showed an improvement in the neuropsychiatric symptoms of schizophrenia at endpoint of paliperidone ER treatment with flexible dosing. Subjects who transitioned to paliperidone ER for the main reason of lack of tolerability or compliance of previous antipsychotic medication or other reasons showed non-inferiority in efficacy of paliperidone (flexible dosing) to previous antipsychotic medication. Over the 6-month treatment period, a consistent improvement of the severity of schizophrenia was observed in the total study population as well as all subgroups.

No unexpected safety findings were reported in this study.