Clinical trial results:
A Randomized, Multicenter, Double-Blind, Weight-Based, Fixed-Dose, Parallel-Group, Placebo-Controlled Study of the Efficacy and Safety of Extended Release Paliperidone for the Treatment of Schizophrenia in Adolescent Subjects, 12 to 17 Years of Age

Summary

EudraCT number	2007-000576-16
Trial protocol	Outside EU/EEA
Global end of trial date	30 March 2009

Results information

Result version number	v2 (current)
This version publication date	29 May 2016
First version publication date	04 July 2015
Version creation reason	• Correction of full data set Review of data

Trial information

Trial identification

Sponsor protocol code	R076477PSZ3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00518323
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, Belgium, Belgium,
Public contact	Turnhoutseweg 30, Belgium, 44 1494658336, Michael B Emanuel, Janssen-Cilag International NV, 44 1494658, memanuel@gcogb.jnj.com
Scientific contact	Turnhoutseweg 30, Belgium, , Michael B Emanuel, Janssen-Cilag International NV, 44 1494658, memanuel@gcogb.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000014-PIP01-07
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 March 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 March 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy, safety, and tolerability of 3 weight-based, fixed-dose groups of paliperidone ER (to fully explore the tolerability range) as compared with placebo in adolescent subjects 12 to 17 years of age, inclusive, with schizophrenia.

Protection of trial subjects:

The safety assessments included laboratory measurements (for example, serum chemistry (including glucose), hematology, urinalysis), Investigation of weight gain and metabolic disturbances, Prolactin, ECG, Vital sign measurements, Physical examinations, Tanner staging, Pregnancy testing, Urine drug screen. The Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson Angus Rating Scale (SARS) were used to assess extrapyramidal symptoms (EPS) and dyskinesia. Adverse events and vital signs were monitored throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 August 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	India: 45
Country: Number of subjects enrolled	Romania: 10
Country: Number of subjects enrolled	Russian Federation: 82
Country: Number of subjects enrolled	Ukraine: 34
Country: Number of subjects enrolled	United States: 30
Worldwide total number of subjects	201
EEA total number of subjects	10

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	201
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started 8 August 2007 in medical clinics located around the world. The study ended on 30 March 2009.

Pre-assignment

Screening details:

Participants who were eligible for the study had their current disallowed psychotropic medications washed out prior to assignment to treatment groups. Participants who violated inclusion criteria before assignment (eg, because they continued to take a disallowed medication) were to be removed from the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Double blinding was used during the 6-week treatment period (i.e., subjects, parent(s), legal guardian(s), investigators and the sponsor remained blinded to the study drug) to reduce potential bias during data collection and evaluation of clinical endpoints.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pali ER Low

Arm description:

Paliperidone ER 1.5 mg for subjects weighing 29 kg and above

Arm type	Experimental
Investigational medicinal product name	INVEGA prolonged release tablets
Investigational medicinal product code	F067
Other name	Paliperidone ER
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were randomly assigned to 1 of the 4 following treatment groups: Oral placebo tablets, Oral paliperidone ER tablet - low dose group (1.5 milligram per day [mg/day] for all participants), Oral paliperidone ER tablet - medium dose group (3 mg/day for Participants weighing between 29 to <51 kg and 6 mg/day for Participants weighing >=51 kg), Oral paliperidone ER tablet - high dose group (6 mg/day for Participants weighing between 29 to <51 kg and 12 mg/day for Participants weighing >=51 kg).

Arm title	Pali ER Medium

Arm description:

Paliperidone ER 3 mg (for subjects weighing between 29 kg and less than 51 kg) or 6 mg (for subjects weighing 51 kg and above)

Arm type	Experimental
Investigational medicinal product name	INVEGA prolonged release tablets
Investigational medicinal product code	F067
Other name	Paliperidone ER
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were randomly assigned to 1 of the 4 following treatment groups: Oral placebo tablets, Oral

paliperidone ER tablet - low dose group (1.5 milligram per day [mg/day] for all participants), Oral paliperidone ER tablet - medium dose group (3 mg/day for Participants weighing between 29 to <51 kg and 6 mg/day for Participants weighing >=51 kg), Oral paliperidone ER tablet - high dose group (6 mg/day for Participants weighing between 29 to <51 kg and 12 mg/day for Participants weighing >=51 kg).

Arm title	Pali ER High

Arm description:

Paliperidone ER 6 mg (for subjects weighing between 29 kg and less than 51 kg) or 12 mg (for subjects weighing 51 kg and above)

Arm type	Experimental
Investigational medicinal product name	INVEGA prolonged release tablets
Investigational medicinal product code	F067
Other name	Paliperidone ER
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were randomly assigned to 1 of the 4 following treatment groups: Oral placebo tablets, Oral paliperidone ER tablet - low dose group (1.5 milligram per day [mg/day] for all participants), Oral paliperidone ER tablet - medium dose group (3 mg/day for Participants weighing between 29 to <51 kg and 6 mg/day for Participants weighing >=51 kg), Oral paliperidone ER tablet - high dose group (6 mg/day for Participants weighing between 29 to <51 kg and 12 mg/day for Participants weighing >=51 kg).

Arm title	Placebo

Arm description:

Matching Placebo to Paliperidone extended release tablet.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were randomly assigned to oral placebo overencapsulated tablets.

Number of subjects in period 1	Pali ER Low	Pali ER Medium	Pali ER High
Started	54	48	48
Completed	35	40	37
Not completed	19	8	11
Adverse Event	1	1	1
Other	3	1	1
Subject Choice (Subject Withdrew Consent)	1	2	4
Lost to follow-up	-	2	1
Lack of efficacy	14	2	4

Number of subjects in period 1	Placebo
Started	51

Completed	26
Not completed	25
Adverse Event	-
Other	-
Subject Choice (Subject Withdrew Consent)	2
Lost to follow-up	3
Lack of efficacy	20

Baseline characteristics

Reporting groups	
Reporting group title	Pali ER Low
Reporting group description:	
Paliperidone ER 1.5 mg for subjects weighing 29 kg and above	
Reporting group title	Pali ER Medium
Reporting group description:	
Paliperidone ER 3 mg (for subjects weighing between 29 kg and less than 51 kg) or 6 mg (for subjects weighing 51 kg and above)	
Reporting group title	Pali ER High
Reporting group description:	
Paliperidone ER 6 mg (for subjects weighing between 29 kg and less than 51 kg) or 12 mg (for subjects weighing 51 kg and above)	
Reporting group title	Placebo
Reporting group description:	
Matching Placebo to Paliperidone extended release tablet.	

Reporting group values	Pali ER Low	Pali ER Medium	Pali ER High
Number of subjects	54	48	48
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	54	48	48
Adults (18-64 years)	0	0	0
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	15.1	15.3	15.5
standard deviation	± 1.5	± 1.6	± 1.6
Title for Gender Units: subjects			
Female	24	17	14
Male	30	31	34

Reporting group values	Placebo	Total	
Number of subjects	51	201	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	51	201	
Adults (18-64 years)	0	0	
From 65 to 84 years	0	0	
85 years and over	0	0	
Title for AgeContinuous Units: years			
arithmetic mean	15.7		
standard deviation	± 1.4	-	

Title for Gender Units: subjects			
Female	28	83	
Male	23	118	

End points

End points reporting groups

Reporting group title	Pali ER Low
Reporting group description:	
Paliperidone ER 1.5 mg for subjects weighing 29 kg and above	
Reporting group title	Pali ER Medium
Reporting group description:	
Paliperidone ER 3 mg (for subjects weighing between 29 kg and less than 51 kg) or 6 mg (for subjects weighing 51 kg and above)	
Reporting group title	Pali ER High
Reporting group description:	
Paliperidone ER 6 mg (for subjects weighing between 29 kg and less than 51 kg) or 12 mg (for subjects weighing 51 kg and above)	
Reporting group title	Placebo
Reporting group description:	
Matching Placebo to Paliperidone extended release tablet.	

Primary: Change in the PANSS Total Score From Baseline to the Last Postrandomization Assessment in the Double-blind Period of the Study

End point title	Change in the PANSS Total Score From Baseline to the Last Postrandomization Assessment in the Double-blind Period of the Study
End point description:	
The Positive and Negative Syndrome Scale (PANSS) measures the severity of psychotic symptoms of schizophrenia. Scores range from 30 to 210, where 30=best and 210=worst. The change in PANSS total score for all eligible subjects was measured from the beginning of the study to the end. The number of participants in the intent-to-treat (ITT) analysis set was used. This set includes patients who received study drug and have at least 1 efficacy measurement. The Last Observation Carried Forward method was used for imputation; ie, the last measure for subjects who ended study early was carried forward as if they completed the study.	
End point type	Primary
End point timeframe:	
6 weeks	

End point values	Pali ER Low	Pali ER Medium	Pali ER High	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	48	47	51
Units: units on a scale				
arithmetic mean (standard deviation)	-9.8 (± 16.31)	-17.3 (± 14.33)	-13.8 (± 15.74)	-7.9 (± 20.15)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

If there were approximately 49 subjects per treatment group who had Week 6 (LOCF or end point) PANSS total measurements, the study was expected to have approximately 80% power to detect a clinically relevant difference of 13.2 points between any paliperidone ER group compared with placebo for the primary outcome measure.

Comparison groups	Pali ER Low v Placebo v Pali ER Medium v Pali ER High
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.508 [2]
Method	ANOVA
Parameter estimate	Median difference (final values)
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.36
upper limit	4.16
Variability estimate	Standard error of the mean
Dispersion value	3.17

Notes:

[1] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.
[2] - The p value was associated with the closed testing procedure using Dunnett’s test.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

If there were approximately 49 subjects per treatment group who had Week 6 (LOCF or end point) PANSS total measurements, the study was expected to have approximately 80% power to detect a clinically relevant difference of 13.2 points between any paliperidone ER group compared with placebo for the primary outcome measure.

Comparison groups	Pali ER Medium v Placebo v Pali ER Low v Pali ER High
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.006 [4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-10.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.58
upper limit	-3.67
Variability estimate	Standard error of the mean
Dispersion value	3.27

Notes:

[3] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.
[4] - The p value was associated with the closed testing procedure using Dunnett’s test.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

If there were approximately 49 subjects per treatment group who had Week 6 (LOCF or end point) PANSS total measurements, the study was expected to have approximately 80% power to detect a

clinically relevant difference of 13.2 points between any paliperidone ER group compared with placebo for the primary outcome measure.

Comparison groups	Pali ER High v Placebo v Pali ER Low v Pali ER Medium
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.086 [6]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.07
upper limit	-0.09
Variability estimate	Standard error of the mean
Dispersion value	3.29

Notes:

[5] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.
[6] - The p value was associated with the closed testing procedure using Dunnett's test.

Secondary: Change From Baseline to End Point in Clinical Global Impression-Severity (CGI-S) Scale

End point title	Change From Baseline to End Point in Clinical Global Impression-Severity (CGI-S) Scale

End point description:

The CGI-S rating scale was used to assess the severity of a subject's overall clinical condition. Scores range from 1 to 7, where 1=best and 7=worst. The number of participants in the intent-to-treat (ITT) analysis set was used. This set includes patients who received study drug and have at least 1 efficacy measurement. The Last Observation Carried Forward method was used for imputation; ie, the last measure for subjects who ended study early was carried forward as if they completed the study.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Pali ER Low	Pali ER Medium	Pali ER High	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	48	47	51
Units: units on a scale				
median (full range (min-max))	0 (-3 to 1)	-1 (-3 to 0)	-1 (-3 to 1)	0 (-3 to 1)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis of the change in the CGI-S score at end point was performed using an analysis of covariance model on the ranks of the change in score at end point with treatment (placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors, and (non-ranked) baseline CGI-S score as a

covariate.

Comparison groups	Pali ER Low v Placebo v Pali ER High v Pali ER Medium
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.968 [7]
Method	ANCOVA

Notes:

[7] - Comparison with placebo was without multiplicity adjustment.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis of the change in the CGI-S score at end point was performed using an analysis of covariance model on the ranks of the change in score at end point with treatment (placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors, and (non-ranked) baseline CGI-S score as a covariate.

Comparison groups	Pali ER Medium v Placebo v Pali ER High v Pali ER Low
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [8]
Method	ANCOVA

Notes:

[8] - Comparison with placebo was without multiplicity adjustment.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Analysis of the change in the CGI-S score at end point was performed using an analysis of covariance model on the ranks of the change in score at end point with treatment (placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors, and (non-ranked) baseline CGI-S score as a covariate.

Comparison groups	Pali ER High v Placebo v Pali ER Low v Pali ER Medium
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021 [9]
Method	ANCOVA

Notes:

[9] - Comparison with placebo was without multiplicity adjustment.

Secondary: Change From Baseline to End Point in Children's Global Assessment (CGAS) Score

End point title	Change From Baseline to End Point in Children's Global Assessment (CGAS) Score

End point description:

The CGAS score assesses psychological, social, and school functioning for children 6 to 17 years of age. Scores range from 1 to 100, where 100=best and 1=worst. The number of participants in the intent-to-treat (ITT) analysis set was used. This set includes patients who received study drug and have at least 1 efficacy measurement. The Last Observation Carried Forward method was used for imputation; ie, the last measure for subjects who ended study early was carried forward as if they completed the study.

End point type	Secondary

End point timeframe:
6 weeks

End point values	Pali ER Low	Pali ER Medium	Pali ER High	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	48	47	51
Units: units on a scale				
arithmetic mean (standard deviation)	4.4 (± 10.72)	13.1 (± 12.07)	8.6 (± 11.18)	5 (± 13.82)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Pali ER Low v Placebo v Pali ER Medium v Pali ER High
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.846 [11]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.54
upper limit	3.73
Variability estimate	Standard error of the mean
Dispersion value	2.1

Notes:

[10] - Used ANCOVA model with treatment (placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.
[11] - Comparison with placebo was without multiplicity adjustment.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Pali ER Medium v Placebo v Pali ER Low v Pali ER High
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.001 [13]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	8.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.28
upper limit	12.82

Variability estimate	Standard error of the mean
Dispersion value	2.17

Notes:

[12] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.
[13] - Comparison with placebo was without multiplicity adjustment.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Pali ER High v Placebo v Pali ER Low v Pali ER Medium
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.067 [15]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	8.33
Variability estimate	Standard error of the mean
Dispersion value	2.18

Notes:

[14] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.
[15] - Comparison with placebo was without multiplicity adjustment.

Secondary: Change From Baseline to End Point in Sleep Visual Analog Scale (VAS) for Quality of Sleep.

End point title	Change From Baseline to End Point in Sleep Visual Analog Scale (VAS) for Quality of Sleep.

End point description:

The sleep VAS for sleep quality is a scale for measuring the quality of sleep experienced by a patient. Scores range from 0 to 100, where 100=best and 0=worst. The number of participants in the intent-to-treat (ITT) analysis set was used. This set includes patients who received study drug and have at least 1 efficacy measurement. The Last Observation Carried Forward method was used for imputation; ie, the last measure for subjects who ended study early was carried forward as if they completed the study.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Pali ER Low	Pali ER Medium	Pali ER High	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	48	47	50
Units: units on a scale				
arithmetic mean (standard deviation)	6.6 (± 24.57)	16 (± 27.06)	14.4 (± 22.72)	-0.3 (± 34.21)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Pali ER Low v Placebo v Pali ER Medium v Pali ER High
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.058 [17]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	8.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	16.56
Variability estimate	Standard error of the mean
Dispersion value	4.27

Notes:

[16] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.
[17] - Comparison with placebo was without multiplicity adjustment.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Pali ER Medium v Placebo v Pali ER Low v Pali ER High
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	< 0.001 [19]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	16.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.08
upper limit	25.43
Variability estimate	Standard error of the mean
Dispersion value	4.4

Notes:

[18] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.
[19] - Comparison with placebo was without multiplicity adjustment.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Pali ER High v Placebo v Pali ER Low v Pali ER Medium
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.003 [21]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	13.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	4.76
upper limit	22.23
Variability estimate	Standard error of the mean
Dispersion value	4.43

Notes:

[20] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.
[21] - Comparison with placebo was without multiplicity adjustment.

Secondary: Change From Baseline to End Point in Sleep VAS for Daytime Drowsiness

End point title	Change From Baseline to End Point in Sleep VAS for Daytime Drowsiness

End point description:

The sleep VAS for daytime drowsiness is a scale for measuring the drowsiness experienced by a patient. Scores range from 0 to 100, where 100=best and 0=worst. The number of participants in the intent-to-treat (ITT) analysis set was used. This set includes patients who received study drug and have at least 1 efficacy measurement. The Last Observation Carried Forward method was used for imputation; ie, the last measure for subjects who ended study early was carried forward as if they completed the study.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Pali ER Low	Pali ER Medium	Pali ER High	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	48	47	50
Units: units on a scale				
arithmetic mean (standard deviation)	-6.2 (± 24.69)	-7.2 (± 25.22)	1 (± 29.55)	-2.8 (± 30.27)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Pali ER Medium v Pali ER Low v Pali ER High
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.237 [23]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.11
upper limit	3.26

Variability estimate	Standard error of the mean
Dispersion value	4.15

Notes:

[22] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.
[23] - Comparison with placebo was without multiplicity adjustment.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Pali ER Medium v Placebo v Pali ER Low v Pali ER High
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.119 [25]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.15
upper limit	1.74
Variability estimate	Standard error of the mean
Dispersion value	4.28

Notes:

[24] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.
[25] - Comparison with placebo was without multiplicity adjustment.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Pali ER High v Placebo v Pali ER Low v Pali ER Medium
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.574 [26]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	6.11
Variability estimate	Standard error of the mean
Dispersion value	4.34

Notes:

[26] - Used ANCOVA model with treatment(placebo, pali ER Low, pali ER Medium, and pali ER High) and country as factors and baseline value as a covariate.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Pali ER Low
Reporting group description:	
Paliperidone ER 1.5 mg for subjects weighing 29 kg and above	
Reporting group title	Pali ER Medium
Reporting group description:	
Paliperidone ER 3 mg (for subjects weighing between 29 kg and less than 51 kg) or 6 mg (for subjects weighing 51 kg and above)	
Reporting group title	Pali ER High
Reporting group description:	
Paliperidone ER 6 mg (for subjects weighing between 29 kg and less than 51 kg) or 12 mg (for subjects weighing 51 kg and above)	
Reporting group title	Placebo
Reporting group description:	
No text entered.	

Serious adverse events	Pali ER Low	Pali ER Medium	Pali ER High
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 54 (3.70%)	1 / 48 (2.08%)	1 / 48 (2.08%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Mallory-Weiss Syndrome			
subjects affected / exposed	0 / 54 (0.00%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic Disorder			

subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 51 (1.96%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Mallory-Weiss Syndrome			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychotic Disorder			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Schizophrenia			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Pali ER Low	Pali ER Medium	Pali ER High
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 54 (35.19%)	20 / 48 (41.67%)	33 / 48 (68.75%)
Investigations			
Weight Increased			
subjects affected / exposed	4 / 54 (7.41%)	2 / 48 (4.17%)	1 / 48 (2.08%)
occurrences (all)	4	2	1
Cardiac disorders			
Tachycardia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 54 (0.00%)	2 / 48 (4.17%)	4 / 48 (8.33%)
occurrences (all)	0	2	5
Nervous system disorders			
Cogwheel Rigidity			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	4 / 48 (8.33%)
occurrences (all)	0	0	7
Akathisia			
subjects affected / exposed	2 / 54 (3.70%)	4 / 48 (8.33%)	8 / 48 (16.67%)
occurrences (all)	2	4	8
Dystonia			
subjects affected / exposed	1 / 54 (1.85%)	1 / 48 (2.08%)	4 / 48 (8.33%)
occurrences (all)	2	1	9
Headache			
subjects affected / exposed	5 / 54 (9.26%)	3 / 48 (6.25%)	5 / 48 (10.42%)
occurrences (all)	5	3	6
Somnolence			
subjects affected / exposed	3 / 54 (5.56%)	7 / 48 (14.58%)	10 / 48 (20.83%)
occurrences (all)	3	8	12
Tremor			
subjects affected / exposed	1 / 54 (1.85%)	4 / 48 (8.33%)	4 / 48 (8.33%)
occurrences (all)	1	7	4
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	4 / 48 (8.33%)
occurrences (all)	0	0	6
Vomiting			

subjects affected / exposed	0 / 54 (0.00%)	3 / 48 (6.25%)	4 / 48 (8.33%)
occurrences (all)	0	3	6
Psychiatric disorders			
Agitation			
subjects affected / exposed	3 / 54 (5.56%)	1 / 48 (2.08%)	0 / 48 (0.00%)
occurrences (all)	4	1	0
Anxiety			
subjects affected / exposed	0 / 54 (0.00%)	0 / 48 (0.00%)	4 / 48 (8.33%)
occurrences (all)	0	0	4
Insomnia			
subjects affected / exposed	5 / 54 (9.26%)	3 / 48 (6.25%)	6 / 48 (12.50%)
occurrences (all)	10	3	8
Schizophrenia			
subjects affected / exposed	5 / 54 (9.26%)	0 / 48 (0.00%)	2 / 48 (4.17%)
occurrences (all)	5	0	2
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 54 (1.85%)	0 / 48 (0.00%)	1 / 48 (2.08%)
occurrences (all)	1	0	1

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 51 (47.06%)		
Investigations			
Weight Increased			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Tachycardia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Cogwheel Rigidity			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Akathisia			

subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0		
Dystonia subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0		
Headache subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2		
Somnolence subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Tremor subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0		
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	6 / 51 (11.76%) 7		
Vomiting subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 6		
Psychiatric disorders			
Agitation subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2		
Anxiety subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2		
Insomnia subjects affected / exposed occurrences (all)	11 / 51 (21.57%) 16		
Schizophrenia subjects affected / exposed occurrences (all)	4 / 51 (7.84%) 4		
Metabolism and nutrition disorders			

Decreased Appetite subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2007	This amendment was done to balance a number of important study design concerns as follows: 1) Lower weight subjects may have nearly double the drug exposure compared with higher weight subjects. Therefore, a regimen for lower weight subjects was milligram per kilogram (mg/kg) with half of the dose strength; 2) a regulatory agency objective requires that the entire dose range be explored. The current design used doses of ranging from 1.5 mg to 12 mg of paliperidone ER and the design allowed testing of the lowest possible dose of 1.5 mg; 3) Each paliperidone ER dose group covered nonoverlapping mg/kg values and thus allowed for a clear interpretation of each paliperidone ER group. The combinations of 3mg and 6 mg for the paliperidone ER medium dose group and that of 6mg and 12mg for the paliperidone ER high dose group wer interpreted as mg/kg over a range of mg/kg values as captured by the mg/kg of those subjects randomly assigned to those categories.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No information about longer-term (ie, >6 weeks) efficacy and safety in adolescents or in young (<12 years) children with schizophrenia. Results with doses less than 1.5 mg or more than 12 mg cannot be extrapolated from the data.

Notes: