Clinical trial results:
A 2-Year, Open-Label, Single-Arm Safety Study of Flexibly Dosed Paliperidone Extended Release (1.5-12 mg/day) in the Treatment of Adolescents (12 to 17 Years of Age) With Schizophrenia

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2007-000577-38
Trial protocol	FI BE EE PL BG Outside EU/EEA
Global end of trial date	18 July 2012

Results information

Result version number	v2 (current)
This version publication date	02 June 2016
First version publication date	30 July 2015
Version creation reason	• Correction of full data set Review of data

Trial information

Trial identification

Sponsor protocol code	R076477-PSZ-3002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00488319
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, 2340 Beerse, Belgium,
Public contact	Janssen-Cilag International NV, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Janssen-Cilag International NV, Janssen-Cilag International NV, ClinicalTrialsEU@its.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	18 July 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 July 2012
Global end of trial reached?	Yes
Global end of trial date	18 July 2012
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 long-term (2-year) safety and tolerability of paliperidone extended release (ER) in at least 100 adolescent subjects (12 to 17 years of age, inclusive) with schizophrenia.

Protection of trial subjects:

This study had an independent Data Safety Monitoring Board (DSMB) to ensure subject safety throughout the study. Safety evaluations included monitoring of clinical laboratory tests (hematology, serum chemistry, lipid levels, fasting glucose, insulin and urinalysis), urine drug screen, vital sign measurements (temperature, pulse, and blood pressure), physical examinations and Tanner Staging, electrocardiograms (ECGs), pregnancy tests, investigation of weight gain, height, waist circumference and metabolic disturbances, monitoring of extrapyramidal symptoms (EPS), Columbia Suicide Severity Rating Scale, C-CASA assessment of potentially suicide-related events and other adverse events (included psychiatric adverse events).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 June 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	India: 64
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 40
Country: Number of subjects enrolled	Poland: 47
Country: Number of subjects enrolled	Romania: 20
Country: Number of subjects enrolled	Russian Federation: 109
Country: Number of subjects enrolled	Ukraine: 48
Country: Number of subjects enrolled	United States: 60

Worldwide total number of subjects	400
EEA total number of subjects	79

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)	397
Adults (18-64 years)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study evaluated the long-term (2 year) safety and tolerability of paliperidone ER in adolescent subjects with schizophrenia. This study was conducted from 27 June 2007 to 18 July 2012 at 55 centers in 10 countries. A total of 400 subjects received at least 1 dose of the study drug and were included in the safety analysis.

Pre-assignment

Screening details:

Subjects enrolled in this study came from three different sources: subjects who enrolled directly, subjects who were randomly assigned to placebo in the R076477PSZ3001 (NCT00518323) study and subjects who were randomly assigned to paliperidone ER in the R076477PSZ3001 (NCT00518323) study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/Pali

Arm description:

Subjects in this group were previously assigned to placebo in the R076477PSZ3001 (NCT00518323) study. They started with an oral dose of 6 milligram (mg) tablets daily, regardless of prior treatment assignment in R076477PSZ3001 (NCT00518323). The initial 6 mg daily dose was increased in increments of 3 mg, not more frequently than once every 5 days until the maximum dose of 12 mg daily was reached. If 12 mg was not well tolerated, then the dose could be reduced down to 9 mg daily. Alternatively the dose could be decreased to 3 mg or 1.5 mg daily, if the initial 6 mg dose was not well tolerated.

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:

Subjects in this group were previously assigned to placebo in the R076477PSZ3001 (NCT00518323) study. They started with an oral dose of 6 mg tablets daily. The initial 6 mg daily dose was increased in increments of 3 mg, not more frequently than once every 5 days until the maximum dose of 12 mg daily was reached.

Arm title	Pali (DB)/Pali

Arm description:

Subjects in this group were previously assigned to paliperidone ER in the R076477PSZ3001 (NCT00518323) study. They started with an oral dose of 6 mg tablets daily, regardless of prior treatment assignment in R076477PSZ3001 (NCT00518323). The initial 6 mg daily dose was increased in increments of 3 mg, not more frequently than once every 5 days until the maximum dose of 12 mg daily was reached. If 12 mg was not well tolerated, then the dose could be reduced down to 9 mg daily. Alternatively the dose could be decreased to 3 mg or 1.5 mg daily, if the initial 6 mg dose was not well tolerated.

Arm type	Experimental

Investigational medicinal product name	Paliperidone ER
Investigational medicinal product code	F071
Other name	INVEGA
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

All enrolled subjects received a starting dose of paliperidone ER 6 mg daily and increased in increments of 3 mg, not more frequently than once every 5 days until the maximum dose of 12 mg daily was reached.

Arm title	Pali (NO DB)/Pali

Arm description:

Subjects in this group were directly enrolled into the study and started with an oral dose of 6 mg tablets daily. The initial 6 mg daily dose was increased in increments of 3 mg, not more frequently than once every 5 days until the maximum dose of 12 mg daily was reached. If 12 mg was not well tolerated, then the dose could be reduced down to 9 mg daily. Alternatively the dose could be decreased to 3 mg or 1.5 mg daily, if the initial 6 mg dose was not well tolerated.

Arm type	Experimental
Investigational medicinal product name	Paliperidone ER
Investigational medicinal product code	F071
Other name	INVEGA
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received an oral dose of 6 mg tablets daily. The initial 6 mg daily dose was increased in increments of 3 mg, not more frequently than once every 5 days until the maximum dose of 12 mg daily was reached.

Number of subjects in period 1	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali
Started	39	118	243
Completed	24	75	121
Not completed	15	43	122
Adverse Event	1	2	23
Other	-	4	12
Subject Choice (Subject Withdrew Consent)	5	20	44
Lost to follow-up	3	5	16
Lack of efficacy	6	12	27

Baseline characteristics

Reporting groups	
Reporting group title	Placebo/Pali

Reporting group description:

Subjects in this group were previously assigned to placebo in the R076477PSZ3001 (NCT00518323) study. They started with an oral dose of 6 milligram (mg) tablets daily, regardless of prior treatment assignment in R076477PSZ3001 (NCT00518323). The initial 6 mg daily dose was increased in increments of 3 mg, not more frequently than once every 5 days until the maximum dose of 12 mg daily was reached. If 12 mg was not well tolerated, then the dose could be reduced down to 9 mg daily. Alternatively the dose could be decreased to 3 mg or 1.5 mg daily, if the initial 6 mg dose was not well tolerated.

Reporting group title	Pali (DB)/Pali

Reporting group description:

Subjects in this group were previously assigned to paliperidone ER in the R076477PSZ3001 (NCT00518323) study. They started with an oral dose of 6 mg tablets daily, regardless of prior treatment assignment in R076477PSZ3001 (NCT00518323). The initial 6 mg daily dose was increased in increments of 3 mg, not more frequently than once every 5 days until the maximum dose of 12 mg daily was reached. If 12 mg was not well tolerated, then the dose could be reduced down to 9 mg daily. Alternatively the dose could be decreased to 3 mg or 1.5 mg daily, if the initial 6 mg dose was not well tolerated.

Reporting group title	Pali (NO DB)/Pali

Reporting group description:

Subjects in this group were directly enrolled into the study and started with an oral dose of 6 mg tablets daily. The initial 6 mg daily dose was increased in increments of 3 mg, not more frequently than once every 5 days until the maximum dose of 12 mg daily was reached. If 12 mg was not well tolerated, then the dose could be reduced down to 9 mg daily. Alternatively the dose could be decreased to 3 mg or 1.5 mg daily, if the initial 6 mg dose was not well tolerated.

Reporting group values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali
Number of subjects	39	118	243
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	39	116	242
Adults (18-64 years)	0	2	1
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	15.8	15.3	15.3
standard deviation	± 1.48	± 1.59	± 1.53
Title for Gender Units: subjects			
Female	21	44	92
Male	18	74	151

Reporting group values	Total		
Number of subjects	400		
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0		
Adolescents (12-17 years)	397		

Adults (18-64 years)	3		
From 65 to 84 years	0		
85 years and over	0		
Title for AgeContinuous Units: years			
arithmetic mean			
standard deviation	-		
Title for Gender Units: subjects			
Female	157		
Male	243		

End points

End points reporting groups

Reporting group title	Placebo/Pali

Reporting group description:

Subjects in this group were previously assigned to placebo in the R076477PSZ3001 (NCT00518323) study. They started with an oral dose of 6 milligram (mg) tablets daily, regardless of prior treatment assignment in R076477PSZ3001 (NCT00518323). The initial 6 mg daily dose was increased in increments of 3 mg, not more frequently than once every 5 days until the maximum dose of 12 mg daily was reached. If 12 mg was not well tolerated, then the dose could be reduced down to 9 mg daily. Alternatively the dose could be decreased to 3 mg or 1.5 mg daily, if the initial 6 mg dose was not well tolerated.

Reporting group title	Pali (DB)/Pali

Reporting group description:

Subjects in this group were previously assigned to paliperidone ER in the R076477PSZ3001 (NCT00518323) study. They started with an oral dose of 6 mg tablets daily, regardless of prior treatment assignment in R076477PSZ3001 (NCT00518323). The initial 6 mg daily dose was increased in increments of 3 mg, not more frequently than once every 5 days until the maximum dose of 12 mg daily was reached. If 12 mg was not well tolerated, then the dose could be reduced down to 9 mg daily. Alternatively the dose could be decreased to 3 mg or 1.5 mg daily, if the initial 6 mg dose was not well tolerated.

Reporting group title	Pali (NO DB)/Pali

Reporting group description:

Subjects in this group were directly enrolled into the study and started with an oral dose of 6 mg tablets daily. The initial 6 mg daily dose was increased in increments of 3 mg, not more frequently than once every 5 days until the maximum dose of 12 mg daily was reached. If 12 mg was not well tolerated, then the dose could be reduced down to 9 mg daily. Alternatively the dose could be decreased to 3 mg or 1.5 mg daily, if the initial 6 mg dose was not well tolerated.

Primary: The Number of Subjects Who Experienced Adverse Events as a Measure of Safety and Tolerability

End point title	The Number of Subjects Who Experienced Adverse Events as a Measure of Safety and Tolerability[1]

End point description:

A serious adverse event (SAE) as defined by the International Conference on Harmonisation (ICH) is any untoward medical occurrence that at any dose results in death, is life-threatening (the subject was at risk of death at the time of the even; it does not refer to an event that hypothetically might have caused death if it were more severe), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Safety analysis set included all subjects who received at least 1 dose of open label study drug.

End point type	Primary

End point timeframe:

Up to 2 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	118	243	
Units: Number of subjects				
Treatment Emergent Adverse Events (TEAEs)	32	88	221	
Possibly-related TEAEs	24	61	185	

One or More Serious TEAEs	9	4	46	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline to Open-label Endpoint in Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Scores - Last Observation Carried Forward (LOCF)

End point title	Change From Open-label Baseline to Open-label Endpoint in Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Scores - Last Observation Carried Forward (LOCF)

End point description:

The PANSS is a medical scale that assesses various symptoms of schizophrenia. The symptoms are rated on a 7-point scale from 1 (absent) to 7 (extreme psychopathology). The total score is the sum of all 30 PANSS items, with a range of 30 (absent) to 210 (extreme ill). Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of open label study drug and had at least 1 postbaseline assessment in open-label phase.

End point type	Secondary

End point timeframe:

Baseline, Week 104 or the last post-baseline assessment

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	117[2]	237[3]	
Units: scores on a scale				
arithmetic mean (standard deviation)	-18.9 (± 21.47)	-12.6 (± 19.92)	-22.4 (± 22.25)	

Notes:

[2] - 'N' signifies number of subjects analysed for this end point.

[3] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline to Open-label Endpoint in the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Based on Marder Factors - LOCF

End point title	Change From Open-label Baseline to Open-label Endpoint in the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Based on Marder Factors - LOCF

End point description:

PANSS scale (30 item) for assessment of schizophrenia provides a total score and scores for 3 subscales, i.e., positive (7 items), negative (7 items), and general psychopathology (16 items) subscales. Each item is scored on a scale of 1 (absent) to 7 (extreme). Positive Factor Score (range: 8 to 56) and Disorganized Thoughts Factor Score (range: 7 to 49): sum of select scores from positive, negative and psychopathology subscales. Negative Factor Score (range: 7 to 49): sum of select scores from negative and general psychopathology subscales. Uncontrolled Hostility/Excitement Factor Score

(range: 4 to 28): sum of select scores from positive and general psychopathology subscales. Anxiety or Depression Factor Score (range: 4 to 28): sum of select scores from general psychopathology subscale. Higher scores indicate worsening. Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of study drug and had at least 1 postbaseline assessment in open-label phase.

End point type	Secondary

End point timeframe:

Baseline, Week 104 or the last post-baseline assessment

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	117[4]	237[5]	
Units: scores on a scale				
arithmetic mean (standard deviation)				
Positive Symptoms	-5.1 (± 6.45)	-3.4 (± 6.11)	-7 (± 7.12)	
Negative Symptoms	-4.3 (± 6.3)	-3.8 (± 4.8)	-5.7 (± 6.68)	
Disorganized Thoughts	-4.8 (± 5.57)	-3.3 (± 4.41)	-4.9 (± 5.52)	
Uncontrolled Hostility/Excitement	-2.6 (± 4.17)	-1.2 (± 4.41)	-2.1 (± 4.68)	
Anxiety/Depression	-2.1 (± 3.35)	-0.9 (± 3.41)	-2.8 (± 3.61)	

Notes:

[4] - 'N' signifies number of subjects analysed for this end point.

[5] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline to Open-label Endpoint in the Clinical Global Impression Severity (CGI-S) Scale - LOCF

End point title	Change From Open-label Baseline to Open-label Endpoint in the Clinical Global Impression Severity (CGI-S) Scale - LOCF

End point description:

The CGI-S rating scale is a 7-point global assessment that measures the clinician's impression of the severity of illness exhibited by a subject. A rating of 1 is equivalent to "Normal, not at all ill" and a rating of 7 is equivalent to "Among the most extremely ill subjects". Higher scores indicate worsening. Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of open label study drug and had at least 1 postbaseline assessment in open-label phase.

End point type	Secondary

End point timeframe:

Baseline, Week 104 or the last post-baseline assessment

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	117[6]	237[7]	
Units: scores on a scale				
median (full range (min-max))	-1 (-3 to 2)	-1 (-3 to 3)	-1 (-5 to 3)	

Notes:

[6] - 'N' signifies number of subjects analysed for this end point.

[7] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline to Open-label Endpoint in the Children's Global Assessment Scale (CGAS) - LOCF

End point title	Change From Open-label Baseline to Open-label Endpoint in the Children's Global Assessment Scale (CGAS) - LOCF

End point description:

The CGAS is a 100 point rating scale which measures the psychological, social, and school functioning for children 6 to 17 years of age. The score ranges from 1 to 100, divided into 10 equal intervals to rate the impairment level of general functioning (poor to superior functioning). Higher scores denote better functioning. Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of open label study drug and had at least 1 postbaseline assessment in open-label phase.

End point type	Secondary

End point timeframe:

Baseline, Week 104 or the last post-baseline assessment

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	117[8]	237[9]	
Units: scores on a scale				
arithmetic mean (standard deviation)	11.3 (± 16.65)	8.7 (± 16.02)	15.6 (± 17.77)	

Notes:

[8] - 'N' signifies number of subjects analysed for this end point.

[9] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Motor Speed Domain Test Variable, Finger Tapping Dominant- and Non-Dominant Hand, Scaled - LOCF

End point title	Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Motor Speed Domain Test Variable, Finger Tapping Dominant- and Non-Dominant Hand, Scaled - LOCF

End point description:

A comprehensive neuropsychological examination that measures different domains of cognitive functioning was provided. They were either assessed as T-scores [mean=50, standard deviation (SD)=10 range 1-100]; z-scores [mean=0, SD=1, and can be positive or negative] or scaled scores [mean=10, SD=3, and can be positive or negative]. The theory-of-mind total score is a raw score that ranges from 1 to 100. Higher scores for all scales denote better performance. Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of open label study drug and had at least 1 postbaseline assessment in open-label phase.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29[10]	88[11]	154[12]	
Units: scores on a scale				
arithmetic mean (standard deviation)				
Finger Tapping Dominant Hand	0.2 (± 1.15)	0.1 (± 1.65)	0.3 (± 1.36)	
Finger Tapping Non Dominant Hand	0.2 (± 1.2)	0.4 (± 2.05)	0.2 (± 1.55)	

Notes:

[10] - 'N' signifies number of subjects analysed for this end point.

[11] - 'N' signifies number of subjects analysed for this end point.

[12] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Attention/Working Memory Domain Test Variable Coding, Scaled - LOCF

End point title	Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Attention/Working Memory Domain Test Variable Coding, Scaled - LOCF

End point description:

A comprehensive neuropsychological examination that measures different domains of cognitive functioning was provided. They were either assessed as T-scores [mean=50, SD =10 range 1-100]; z-scores [mean=0, SD=1, and can be positive or negative] or scaled scores [mean=10, SD=3, and can be positive or negative]. The theory-of-mind total score is a raw score that ranges from 1 to 100. Higher scores for all scales denote better performance. Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of open label study drug and had at least 1 postbaseline assessment in open-label phase.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27[13]	90[14]	143[15]	
Units: scores on a scale				
arithmetic mean (standard deviation)	1.9 (± 3.25)	1.5 (± 2.54)	0.1 (± 2.6)	

Notes:

[13] - 'N' signifies number of subjects analysed for this end point.

[14] - 'N' signifies number of subjects analysed for this end point.

[15] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Attention/Working Memory Domain Test Variable Digit Span, Scaled - LOCF

End point title	Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Attention/Working Memory Domain Test Variable Digit Span, Scaled - LOCF

End point description:

A comprehensive neuropsychological examination that measures different domains of cognitive functioning was provided. They were either assessed as T-scores [mean=50, SD=10 range 1-100]; z-scores [mean=0, SD=1, and can be positive or negative] or scaled scores [mean=10, SD=3, and can be positive or negative]. The theory-of-mind total score is a raw score that ranges from 1 to 100. Higher scores for all scales denote better performance. Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of open label study drug and had at least 1 postbaseline assessment in open-label phase.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28[16]	95[17]	159[18]	
Units: scores on a scale				
arithmetic mean (standard deviation)	0.9 (± 2.42)	0.8 (± 2.81)	0.8 (± 2.71)	

Notes:

[16] - 'N' signifies number of subjects analysed for this end point.

[17] - 'N' signifies number of subjects analysed for this end point.

[18] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline to Open-label - Cognitive Domain: Verbal Learning and Memory Domain Test Variable Wide Range Assessment of Memory and Learning Story - Total, Scaled - LOCF

End point title	Change From Open-label Baseline to Open-label - Cognitive Domain: Verbal Learning and Memory Domain Test Variable Wide Range Assessment of Memory and Learning Story - Total, Scaled - LOCF

End point description:

A comprehensive neuropsychological examination that measures different domains of cognitive functioning was provided. They were either assessed as T-scores [mean=50, SD=10 range 1-100]; z-scores [mean=0, SD=1, and can be positive or negative] or scaled scores [mean=10, SD=3, and can be positive or negative]. The theory-of-mind total score is a raw score that ranges from 1 to 100. Higher scores for all scales denote better performance. Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of open label study drug and had at least 1 postbaseline assessment in open-label phase. SD for Placebo/Paliperidone group in this end point was not estimable because only one subject was analysed for this end point. Therefore, value mentioned for SD is 99999= NA (Not Applicable).

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1[19]	9[20]	17[21]	
Units: scores on a scale				
arithmetic mean (standard deviation)	0 (± 99999)	0.6 (± 3.57)	1.7 (± 1.36)	

Notes:

[19] - 'N' signifies number of subjects analysed for this end point.

[20] - 'N' signifies number of subjects analysed for this end point.

[21] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Verbal Learning and Memory Domain Test Variable California Verbal Learning Test-Total Trials, Scaled - LOCF

End point title	Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Verbal Learning and Memory Domain Test Variable California Verbal Learning Test-Total Trials, Scaled - LOCF

End point description:

A comprehensive neuropsychological examination that measures different domains of cognitive functioning was provided. They were either assessed as T-scores [mean=50, SD=10 range 1-100]; z-scores [mean=0, SD=1, and can be positive or negative] or scaled scores [mean=10, SD=3, and can be positive or negative]. The theory-of-mind total score is a raw score that ranges from 1 to 100. Higher scores for all scales denote better performance. Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of open label study drug and had at least 1 postbaseline assessment in open-label phase. SD for group Placebo/Paliperidone was not estimable because only one subject was analysed for this end point. Therefore, value mentioned for SD i.e. 99999= NA (Not Applicable).

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1[22]	11[23]	18[24]	
Units: scores on a scale				
arithmetic mean (standard deviation)	29 (± 99999)	3.5 (± 12.29)	8.2 (± 12.19)	

Notes:

[22] - 'N' signifies number of subjects analysed for this end point.

[23] - 'N' signifies number of subjects analysed for this end point.

[24] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Visual Learning and Memory Domain Test Variable, Rey Complex Figure Test - Total, Scaled - LOCF

End point title	Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Visual Learning and Memory Domain Test Variable, Rey Complex Figure Test - Total, Scaled - LOCF

End point description:

A comprehensive neuropsychological examination that measures different domains of cognitive functioning was provided. They were either assessed as T-scores [mean=50, SD=10 range 1-100]; z-scores [mean=0, SD=1, and can be positive or negative] or scaled scores [mean=10, SD=3, and can be positive or negative]. The theory-of-mind total score is a raw score that ranges from 1 to 100. Higher scores for all scales denote better performance. Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of open label study drug and had at least 1 postbaseline assessment in open-label phase.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29[25]	92[26]	150[27]	
Units: scores on a scale				
arithmetic mean (standard deviation)	-0.5 (± 1.56)	-0.3 (± 2.02)	0.3 (± 2.39)	

Notes:

[25] - 'N' signifies number of subjects analysed for this end point.

[26] - 'N' signifies number of subjects analysed for this end point.

[27] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open Label Baseline to Open Label Endpoint - Cognitive Domain: Social Cognition Domain Test Variable - Theory of Mind-Total - LOCF

End point title	Change From Open Label Baseline to Open Label Endpoint - Cognitive Domain: Social Cognition Domain Test Variable - Theory of Mind-Total - LOCF

End point description:

A comprehensive neuropsychological examination that measures different domains of cognitive functioning was provided. They were either assessed as T-scores [mean=50, SD=10 range 1-100]; z-scores [mean=0, SD=1, and can be positive or negative] or scaled scores [mean=10, SD=3, and can be positive or negative]. The theory-of-mind total score is a raw score that ranges from 1 to 100. Higher scores for all scales denote better performance. Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of open label study drug and had at least 1 postbaseline assessment in open-label phase.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29[28]	91[29]	149[30]	
Units: scores on a scale				
arithmetic mean (standard deviation)	3.4 (± 7.04)	4.1 (± 6.68)	5.6 (± 9.2)	

Notes:

[28] - 'N' signifies number of subjects analysed for this end point.

[29] - 'N' signifies number of subjects analysed for this end point.

[30] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open Label Baseline to Open Label Endpoint - Cognitive Domain: Speed of Processing Domain Test Variable Trials Part A Time: Scaled - LOCF

End point title	Change From Open Label Baseline to Open Label Endpoint - Cognitive Domain: Speed of Processing Domain Test Variable Trials Part A Time: Scaled - LOCF

End point description:

A comprehensive neuropsychological examination that measures different domains of cognitive functioning was provided. They were either assessed as T-scores [mean=50, SD=10 range 1-100]; z-scores [mean=0, SD=1, and can be positive or negative] or scaled scores [mean=10, SD=3, and can be positive or negative]. The theory-of-mind total score is a raw score that ranges from 1 to 100. Higher scores for all scales denote better performance. Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of open label study drug and had at least 1 postbaseline assessment in open-label phase.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[31]	15[32]	21[33]	
Units: scores on a scale				
arithmetic mean (standard deviation)	1.8 (± 1.06)	-2.3 (± 4.97)	1.5 (± 7.66)	

Notes:

[31] - 'N' signifies number of subjects analysed for this end point.

[32] - 'N' signifies number of subjects analysed for this end point.

[33] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Speed of Processing Domain Test Variable Child Color Trials Test 1 Time: Scaled - LOCF

End point title	Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Speed of Processing Domain Test Variable Child Color Trials Test 1 Time: Scaled - LOCF

End point description:

A comprehensive neuropsychological examination that measures different domains of cognitive functioning was provided. They were either assessed as T-scores [mean=50, SD =10 range 1-100]; z-scores [mean=0, SD=1, and can be positive or negative] or scaled scores [mean=10, SD=3, and can be positive or negative]. The theory-of-mind total score is a raw score that ranges from 1 to 100. Higher scores for all scales denote better performance. Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of open label study drug and had at least 1 postbaseline assessment in open-label phase.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21[34]	58[35]	101[36]	
Units: scores on a scale				
arithmetic mean (standard deviation)	0 (± 20.82)	3.6 (± 11.9)	6.2 (± 14.41)	

Notes:

[34] - 'N' signifies number of subjects analysed for this end point.

[35] - 'N' signifies number of subjects analysed for this end point.

[36] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Speed of Processing Domain Test Variable Phonetic Verbal Fluency: Scaled - LOCF

End point title	Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Speed of Processing Domain Test Variable Phonetic Verbal Fluency: Scaled - LOCF

End point description:

A comprehensive neuropsychological examination that measures different domains of cognitive functioning was provided. They were either assessed as T-scores [mean=50, SD =10 range 1-100]; z-scores [mean=0, SD=1, and can be positive or negative] or scaled scores [mean=10, SD=3, and can be positive or negative]. The theory-of-mind total score is a raw score that ranges from 1 to 100. Higher scores for all scales denote better performance. Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of open label study drug and had at least 1 postbaseline assessment in open-label phase.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21[37]	78[38]	79[39]	
Units: scores on a scale				
arithmetic mean (standard deviation)	0.3 (± 1.48)	0.2 (± 1.07)	0.5 (± 1.09)	

Notes:

[37] - 'N' signifies number of subjects analysed for this end point.

[38] - 'N' signifies number of subjects analysed for this end point.

[39] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Speed of Processing Domain Test Variable Semantic Verbal Fluency, Scaled - LOCF

End point title	Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Speed of Processing Domain Test Variable Semantic Verbal Fluency, Scaled - LOCF

End point description:

A comprehensive neuropsychological examination that measures different domains of cognitive functioning was provided. They were either assessed as T-scores [mean=50, SD=10 range 1-100]; z-scores [mean=0, SD=1, and can be positive or negative] or scaled scores [mean=10, SD=3, and can be positive or negative]. The theory-of-mind total score is a raw score that ranges from 1 to 100. Higher scores for all scales denote better performance. Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of open label study drug and had at least 1 postbaseline assessment in open-label phase.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20[40]	76[41]	78[42]	
Units: scores on a scale				
arithmetic mean (standard deviation)	0.2 (± 1.23)	0.1 (± 0.82)	0.2 (± 0.9)	

Notes:

[40] - 'N' signifies number of subjects analysed for this end point.

[41] - 'N' signifies number of subjects analysed for this end point.

[42] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Executive Functioning (Reasoning and Problem Solving) Domain Test Variable, Trials Part B Time, Scaled - LOCF

End point title	Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Executive Functioning (Reasoning and

	Problem Solving) Domain Test Variable, Trials Part B Time, Scaled - LOCF

End point description:

A comprehensive neuropsychological examination that measures different domains of cognitive functioning was provided. They were either assessed as T-scores [mean=50, SD=10 range 1-100]; z-scores [mean=0, SD=1, and can be positive or negative] or scaled scores [mean=10, SD=3, and can be positive or negative]. The theory-of-mind total score is a raw score that ranges from 1 to 100. Higher scores for all scales denote better performance. Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of open label study drug and had at least 1 postbaseline assessment in open-label phase.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[43]	15[44]	18[45]	
Units: scores on a scale				
arithmetic mean (standard deviation)	()	0.2 (± 2.67)	0.7 (± 2.53)	

Notes:

[43] - No subjects was analysed in Placebo/Paliperidone group for this end point.

[44] - 'N' signifies number of subjects analysed for this end point.

[45] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Executive Functioning (Reasoning and Problem Solving) Domain Test Variable - Wisconsin Card Sort Test-Total Errors: Scaled - LOCF

End point title	Change From Open-label Baseline to Open-label Endpoint - Cognitive Domain: Executive Functioning (Reasoning and Problem Solving) Domain Test Variable - Wisconsin Card Sort Test-Total Errors: Scaled - LOCF

End point description:

A comprehensive neuropsychological examination that measures different domains of cognitive functioning was provided. They were either assessed as T-scores [mean=50, SD=10 range 1-100]; z-scores [mean=0, SD=1, and can be positive or negative] or scaled scores [mean=10, SD=3, and can be positive or negative]. The theory-of-mind total score is a raw score that ranges from 1 to 100. Higher scores for all scales denote better performance. Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of open label study drug and had at least 1 postbaseline assessment in open-label phase.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15[46]	66[47]	109[48]	
Units: scores on a scale				
arithmetic mean (standard deviation)	4.3 (± 11.13)	4.6 (± 11.09)	7 (± 13.16)	

Notes:

[46] - 'N' signifies number of subjects analysed for this end point.

[47] - 'N' signifies number of subjects analysed for this end point.

[48] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline to Open-label Endpoint in the Sleep Visual Analog Scale (VAS): Quality of Sleep - LOCF

End point title	Change From Open-label Baseline to Open-label Endpoint in the Sleep Visual Analog Scale (VAS): Quality of Sleep - LOCF

End point description:

Sleep VAS is a self-administered scale that rates the quality of sleep and daytime drowsiness. Subjects make a mark on a line to represent how well they have slept in the previous 7 days (“very badly” to “very well”) and how often they have felt drowsy within the previous 7 days (“not at all” to “all the time”). The score for each item ranges from 0 to 100 millimeter (mm). For quality of sleep, a score of 0 indicates
“Very badly” and a score of 100 indicates “Very well.” For daytime drowsiness, a score of 0 indicates “Not at all” and a score of 100 indicates “All the time.” Improvement of the condition is indicated by the positive change for the quality of sleep and the negative change for the daytime drowsiness. Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of open label study drug and had at least 1 postbaseline assessment in open-label phase.

End point type	Secondary

End point timeframe:

Baseline, Week 104 or the last post-baseline assessment

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36[49]	116[50]	223[51]	
Units: scores on a scale				
arithmetic mean (standard deviation)	8.2 (± 30.51)	2.7 (± 18.48)	9.8 (± 32.47)	

Notes:

[49] - 'N' signifies number of subjects analysed for this end point.

[50] - 'N' signifies number of subjects analysed for this end point.

[51] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Open-label Baseline to Open-label Endpoint in the Sleep Visual Analog Scale (VAS): Daytime Drowsiness - LOCF

End point title	Change From Open-label Baseline to Open-label Endpoint in the Sleep Visual Analog Scale (VAS): Daytime Drowsiness - LOCF

End point description:

Sleep VAS is a self-administered scale that rates the quality of sleep and daytime drowsiness. Subjects make a mark on a line to represent how well they have slept in the previous 7 days (“very badly” to “very well”) and how often they have felt drowsy within the previous 7 days (“not at all” to “all the time”). The score for each item ranges from 0 to 100 mm. For quality of sleep, a score of 0 indicates “Very badly” and a score of 100 indicates “Very well.” For daytime drowsiness, a score of 0 indicates “Not at all” and a score of 100 indicates “All the time.” Improvement of the condition is indicated by the positive change for the quality of sleep and negative change for the daytime drowsiness. Efficacy analysis set included all ITT open-label subjects who received at least 1 dose of open label study drug and had at least 1 postbaseline assessment in open-label phase.

End point type	Secondary

End point timeframe:

Baseline, Week 104 or the last post-baseline assessment

End point values	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36[52]	116[53]	223[54]	
Units: scores on a scale				
arithmetic mean (standard deviation)	-7.4 (± 18.83)	-5.1 (± 22.39)	-3.9 (± 32.3)	

Notes:

[52] - 'N' signifies number of subjects analysed for this end point.

[53] - 'N' signifies number of subjects analysed for this end point.

[54] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 2 years

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Placebo/Pali

Reporting group description:

Patients in this group were previously assigned to placebo in the R076477PSZ3001 (NCT00518323) study. They started with an oral dose of 6 mg tablets daily, regardless of prior treatment assignment in R076477PSZ3001 (NCT00518323). The initial 6 mg daily dose was increased in increments of 3 mg, not more frequently than once every 5 days until the maximum dose of 12 mg daily was reached. If 12 mg was not well tolerated, then the dose could be reduced down to 9 mg daily. Alternatively the dose could be decreased to 3 mg or 1.5 mg daily, if the initial 6 mg dose was not well tolerated.

Reporting group title	Pali (DB)/Pali

Reporting group description:

Patients in this group were previously assigned to paliperidone extended-release in the R076477PSZ3001 (NCT00518323) study. They started with an oral dose of 6 mg tablets daily, regardless of prior treatment assignment in R076477PSZ3001 (NCT00518323). The initial 6 mg daily dose was increased in increments of 3 mg, not more frequently than once every 5 days until the maximum dose of 12 mg daily was reached. If 12 mg was not well tolerated, then the dose could be reduced down to 9 mg daily. Alternatively the dose could be decreased to 3 mg or 1.5 mg daily, if the initial 6 mg dose was not well tolerated.

Reporting group title	Pali (NO DB)/Pali

Reporting group description:

Patients in this group were directly enrolled into the study and started with an oral dose of 6 mg tablets daily. The initial 6 mg daily dose was increased in increments of 3 mg, not more frequently than once every 5 days until the maximum dose of 12 mg daily was reached. If 12 mg was not well tolerated, then the dose could be reduced down to 9 mg daily. Alternatively the dose could be decreased to 3 mg or 1.5 mg daily, if the initial 6 mg dose was not well tolerated.

Serious adverse events	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 39 (23.08%)	4 / 118 (3.39%)	46 / 243 (18.93%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Frostbite			
subjects affected / exposed	0 / 39 (0.00%)	1 / 118 (0.85%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Compression Fracture			

subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Limb Fracture			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dystonia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	2 / 243 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokinesia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oromandibular Dystonia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech Disorder			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Lymphadenitis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 118 (0.00%)	0 / 243 (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
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	1 / 39 (2.56%)	1 / 118 (0.85%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Ingrowing Nail			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Adjustment Disorder			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aggression			

subjects affected / exposed	0 / 39 (0.00%)	1 / 118 (0.85%)	3 / 243 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	0 / 39 (0.00%)	1 / 118 (0.85%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	1 / 39 (2.56%)	0 / 118 (0.00%)	3 / 243 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delusion			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	2 / 243 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delusion of Grandeur			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed Mood			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressive Symptom			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flight of Ideas			

subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	2 / 243 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination, Auditory			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	2 / 243 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional Self-Injury			
subjects affected / exposed	1 / 39 (2.56%)	0 / 118 (0.00%)	0 / 243 (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
Mania			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oppositional Defiant Disorder			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paranoia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 118 (0.85%)	0 / 243 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic Disorder			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	2 / 243 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			

subjects affected / exposed	7 / 39 (17.95%)	2 / 118 (1.69%)	21 / 243 (8.64%)
occurrences causally related to treatment / all	0 / 8	0 / 2	4 / 30
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia, Paranoid Type			
subjects affected / exposed	1 / 39 (2.56%)	0 / 118 (0.00%)	2 / 243 (0.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia, Undifferentiated Type			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Self Injurious Behaviour			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal Ideation			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	7 / 243 (2.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide Attempt			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	3 / 243 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tension			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			

subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal Stiffness			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	1 / 243 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	2 / 243 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 118 (0.00%)	0 / 243 (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

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

Non-serious adverse events	Placebo/Pali	Pali (DB)/Pali	Pali (NO DB)/Pali
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 39 (66.67%)	74 / 118 (62.71%)	192 / 243 (79.01%)
Investigations			
Weight Increased			
subjects affected / exposed	2 / 39 (5.13%)	12 / 118 (10.17%)	59 / 243 (24.28%)
occurrences (all)	2	12	72
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 39 (5.13%)	1 / 118 (0.85%)	3 / 243 (1.23%)
occurrences (all)	2	1	3
Tachycardia			
subjects affected / exposed	2 / 39 (5.13%)	1 / 118 (0.85%)	8 / 243 (3.29%)
occurrences (all)	2	1	9
Nervous system disorders			

Akathisia			
subjects affected / exposed	0 / 39 (0.00%)	10 / 118 (8.47%)	42 / 243 (17.28%)
occurrences (all)	0	14	49
Dizziness			
subjects affected / exposed	4 / 39 (10.26%)	8 / 118 (6.78%)	13 / 243 (5.35%)
occurrences (all)	4	8	15
Dystonia			
subjects affected / exposed	1 / 39 (2.56%)	6 / 118 (5.08%)	13 / 243 (5.35%)
occurrences (all)	3	11	17
Headache			
subjects affected / exposed	4 / 39 (10.26%)	9 / 118 (7.63%)	46 / 243 (18.93%)
occurrences (all)	5	12	74
Sedation			
subjects affected / exposed	1 / 39 (2.56%)	0 / 118 (0.00%)	14 / 243 (5.76%)
occurrences (all)	1	0	18
Somnolence			
subjects affected / exposed	10 / 39 (25.64%)	18 / 118 (15.25%)	45 / 243 (18.52%)
occurrences (all)	10	27	57
Tremor			
subjects affected / exposed	1 / 39 (2.56%)	12 / 118 (10.17%)	31 / 243 (12.76%)
occurrences (all)	2	15	40
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 39 (7.69%)	3 / 118 (2.54%)	3 / 243 (1.23%)
occurrences (all)	3	3	3
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	0 / 39 (0.00%)	2 / 118 (1.69%)	14 / 243 (5.76%)
occurrences (all)	0	2	22
Nausea			
subjects affected / exposed	1 / 39 (2.56%)	3 / 118 (2.54%)	27 / 243 (11.11%)
occurrences (all)	1	3	32
Salivary Hypersecretion			
subjects affected / exposed	2 / 39 (5.13%)	9 / 118 (7.63%)	22 / 243 (9.05%)
occurrences (all)	3	11	28
Vomiting			

subjects affected / exposed	0 / 39 (0.00%)	3 / 118 (2.54%)	22 / 243 (9.05%)
occurrences (all)	0	4	33
Reproductive system and breast disorders			
Galactorrhoea			
subjects affected / exposed	3 / 39 (7.69%)	4 / 118 (3.39%)	9 / 243 (3.70%)
occurrences (all)	3	5	11
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	2 / 39 (5.13%)	2 / 118 (1.69%)	7 / 243 (2.88%)
occurrences (all)	2	2	8
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	14 / 243 (5.76%)
occurrences (all)	0	0	15
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 39 (10.26%)	7 / 118 (5.93%)	14 / 243 (5.76%)
occurrences (all)	5	8	17
Insomnia			
subjects affected / exposed	7 / 39 (17.95%)	11 / 118 (9.32%)	40 / 243 (16.46%)
occurrences (all)	10	18	53
Schizophrenia			
subjects affected / exposed	2 / 39 (5.13%)	10 / 118 (8.47%)	14 / 243 (5.76%)
occurrences (all)	3	12	18
Suicidal Ideation			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	30 / 243 (12.35%)
occurrences (all)	0	0	48
Musculoskeletal and connective tissue disorders			
Muscle Rigidity			
subjects affected / exposed	1 / 39 (2.56%)	6 / 118 (5.08%)	19 / 243 (7.82%)
occurrences (all)	2	6	22
Musculoskeletal Stiffness			
subjects affected / exposed	0 / 39 (0.00%)	0 / 118 (0.00%)	14 / 243 (5.76%)
occurrences (all)	0	0	22
Infections and infestations			

Bronchitis			
subjects affected / exposed	2 / 39 (5.13%)	1 / 118 (0.85%)	2 / 243 (0.82%)
occurrences (all)	2	2	2
Nasopharyngitis			
subjects affected / exposed	3 / 39 (7.69%)	18 / 118 (15.25%)	32 / 243 (13.17%)
occurrences (all)	4	27	47
Rhinitis			
subjects affected / exposed	2 / 39 (5.13%)	2 / 118 (1.69%)	9 / 243 (3.70%)
occurrences (all)	2	2	9
Metabolism and nutrition disorders			
Increased Appetite			
subjects affected / exposed	2 / 39 (5.13%)	3 / 118 (2.54%)	9 / 243 (3.70%)
occurrences (all)	2	3	11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2007	Amendment INT-1: Added clarification that an effective dose had to be 6 mg or less; the period of dose increments was modified; and the minimum weight required for inclusion in the study was lowered.
11 June 2008	Amendment INT 2: Extended the study duration from 6 months to 2 years; increased the number of visits, blood draws, evaluations, and dosing for the extended study duration; increased the sample size from 300 to 400 subjects; testing for testosterone in men was added to assess long-term endocrine effects; analyses were planned to be performed when 100 subjects completed at least 6 months of treatment and at the end of the 2-year study.
13 May 2009	Amendment INT-3: Included the C-SSRS as a safety assessment for Visits 2 to 19.
01 April 2010	Amendment INT-4: A statement was added which specified that stadiometers were required to measure subjects' height. At the time of the amendment, 369 subjects were enrolled in the study.
14 May 2010	Amendment INT-5: Negative symptoms were added as a secondary end point. At the time of the amendment, 382 subjects were enrolled in the study.
04 April 2011	Amendment INT-6: Additional antiparkinsonian drugs (i.e. trihexyphenidyl, diphenhydramine, etc.) were added as alternatives to benztropine and biperiden for managing treatment-emergent EPS; the timing of study drug intake was adjusted based on subject tolerability and logistic reasons; and the eCRF completion period was changed from within 2 days to 3 days following a subject's visit. At the time of the amendment, all subjects were enrolled in the study.

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.

The study was an open label study. Limitations also included the lack of a concurrent placebo group and small number of subjects in the lower age group.

Notes: