



Clinical trial results:

A Randomized, Multicenter, Double-Blind, Non-inferiority Study of Paliperidone Palmitate 3 Month and 1 Month Formulations for the Treatment of Subjects with Schizophrenia

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2011-004889-15
Trial protocol	CZ ES BE DE PT AT SE DK SK FI GR BG
Global end of trial date	02 March 2015

Results information

Result version number	v1 (current)
This version publication date	04 June 2016
First version publication date	04 June 2016

Trial information

Trial identification

Sponsor protocol code	R092670PSY3011
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01515423
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route 202, Raritan, United States, NJ 08869
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 February 2015
Global end of trial reached?	Yes
Global end of trial date	02 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to demonstrate in subjects stabilized on paliperidone palmitate 1 month formulation (PP1M), that paliperidone palmitate 3 month formulation (PP3M) was not less effective than PP1M in the treatment of symptoms of schizophrenia, based on the Kaplan-Meier 48-week cumulative estimate of survival (For example: percentage of subjects remaining relapse free).

Protection of trial subjects:

The trial was performed in accordance with the principles of good clinical practices [GCP] as outlined in 21 code of federal regulations [CFR] Parts 50, 56, and 312 and the Declaration of Helsinki and its subsequent revisions, and the European Union Clinical Trials Directive that are consistent with Good Clinical Practices and applicable regulatory requirements. During the study, various safety evaluations were performed at different timepoints like clinical laboratory assessments (hematology, serum chemistry, metabolic chemistry and urinalysis), vital signs, 12-lead electrocardiograms (ECGs) and physical examination, all adverse events were reported from signing the informed consent until the follow-up visit.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 April 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 37
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 23
Country: Number of subjects enrolled	Bulgaria: 38
Country: Number of subjects enrolled	Brazil: 31
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	China: 296
Country: Number of subjects enrolled	Czech Republic: 69
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Spain: 42
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Greece: 14
Country: Number of subjects enrolled	Hungary: 51
Country: Number of subjects enrolled	Japan: 175

Country: Number of subjects enrolled	Korea, Republic of: 19
Country: Number of subjects enrolled	Mexico: 19
Country: Number of subjects enrolled	Poland: 56
Country: Number of subjects enrolled	Portugal: 30
Country: Number of subjects enrolled	Romania: 20
Country: Number of subjects enrolled	Russian Federation: 177
Country: Number of subjects enrolled	Slovakia: 23
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Taiwan: 20
Country: Number of subjects enrolled	Ukraine: 72
Country: Number of subjects enrolled	United States: 167
Worldwide total number of subjects	1429
EEA total number of subjects	398

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)	0
Adults (18-64 years)	1408
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

1429 subjects received at least 1 dose of the study agent in the Open label Phase, out of which 1016 subjects were randomized into the Double blind Phase (Safety population).

Period 1

Period 1 title	Open-Label
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Open-Label: Paliperidone Palmitate 1 month (PP1M)
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Arm description:

Subjects received Paliperidone Palmitate 1 month formulation (PP1M) in a dose of 150 milligram equivalent (mg eq.) on Day 1 and 100 mg eq. on Day 8, both as an injection in the deltoid muscle. The injections at Week 5 (Day 36) and Week 9 (Day 64) given in either the deltoid or gluteal muscle and were flexibly dosed (50, 75, 100, or 150 mg eq.). At Week 13 (Day 92) subjects received the same dose of PP1M that was administered at Week 9.

Arm type	Experimental
Investigational medicinal product name	Paliperidone Palmitate
Investigational medicinal product code	R092670
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received Paliperidone Palmitate 1 month formulation (PP1M) administered via intramuscular route in a dose of 150 milligram equivalent (mg eq.) on Day 1 and 100 mg eq. on Day 8. At Week 5 (Day 36) and Week 9 (Day 64) given in flexibly dosed (50, 75, 100, or 150 mg eq.). At Week 13 (Day 92) subjects received the same dose of PP1M that was administered at Week 9.

Number of subjects in period 1	Open-Label: Paliperidone Palmitate 1 month (PP1M)
Started	1429
Completed	1016
Not completed	413
Adverse event, serious fatal	2
Consent withdrawn by subject	118
Failed to meet randomization criteria	70
Adverse event, non-fatal	40
Unspecified	28
Adverse event, serious non-fatal	17

Lost to follow-up	21
Lack of efficacy	117

Period 2

Period 2 title	Double-Blind
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind:Paliperidone Palmitate 3 month (PP3M) Formulation

Arm description:

Subjects received Paliperidone Palmitate 3month formulation (PP3M) in a fixed dose of 3.5 fold multiple of the PP1M dose administered at Week 13, that is subjects received fixed dose injections of PP3M (175, 263, 350, or 525 mg eq.) on Week 17, 29, 41, and 53 as injection in deltoid muscle or gluteal muscle. Also the subjects received placebo injection (intralipid) at weeks 21, 25, 33 during the gap period, when they were not receiving PP3M to maintain the blind.

Arm type	Experimental
Investigational medicinal product name	Paliperidone Palmitate
Investigational medicinal product code	R092670
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received Paliperidone Palmitate 3 month formulation (PP3M) administered via intramuscular route in a fixed dose fixed dose injections of PP3M (175, 263, 350, or 525 mg eq.) on Week 17, 29, 41, and 53.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received placebo injection (intralipid) at weeks 21, 25, 33 during the gap period, when they were not receiving PP3M to maintain the blind.

Arm title	Double-Blind:Paliperidone Palmitate 1 month (PP1M) Formulation
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Arm description:

Subjects received Paliperidone Palmitate 1 month formulation (PP1M) in a fixed dose that was administered at Week 9 at every month for 48 weeks, that is, subjects received fixed dose injections of PP1M (50, 75, 100, or 150 mg eq.) as injection on deltoid muscle or gluteal muscle.

Arm type	Experimental
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Investigational medicinal product name	Paliperidone Palmitate
Investigational medicinal product code	R092670
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received Paliperidone Palmitate 1 month formulation (PP1M) administered via intramuscular route in a fixed dose injections of PP1M (50, 75, 100, or 150 mg eq.).

Number of subjects in period 2	Double-Blind:Paliperidone Palmitate 3 month (PP3M) Formulation	Double-Blind:Paliperidone Palmitate 1 month (PP1M) Formulation
Started	504	512
Completed	422	420
Not completed	82	92
Adverse event, serious fatal	1	2
Consent withdrawn by subject	50	53
Adverse event, non-fatal	14	10
Pregnancy	2	-
Unspecified	6	12
Adverse event, serious non-fatal	1	3
Blind broken by investigator	1	-
Lost to follow-up	7	12

Baseline characteristics

Reporting groups

Reporting group title	Open-Label: Paliperidone Palmitate 1 month (PP1M)
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Reporting group description:

Subjects received Paliperidone Palmitate 1 month formulation (PP1M) in a dose of 150 milligram equivalent (mg eq.) on Day 1 and 100 mg eq. on Day 8, both as an injection in the deltoid muscle. The injections at Week 5 (Day 36) and Week 9 (Day 64) given in either the deltoid or gluteal muscle and were flexibly dosed (50, 75, 100, or 150 mg eq.). At Week 13 (Day 92) subjects received the same dose of PP1M that was administered at Week 9.

Reporting group values	Open-Label: Paliperidone Palmitate 1 month (PP1M)	Total	
Number of subjects	1429	1429	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1408	1408	
From 65 to 84 years	21	21	
85 years and over	0	0	
Title for AgeContinuous Units: years			
arithmetic mean	38.4		
standard deviation	± 11.86	-	
Title for Gender Units: subjects			
Female	647	647	
Male	782	782	

End points

End points reporting groups

Reporting group title	Open-Label: Paliperidone Palmitate 1 month (PP1M)
Reporting group description: Subjects received Paliperidone Palmitate 1 month formulation (PP1M) in a dose of 150 milligram equivalent (mg eq.) on Day 1 and 100 mg eq. on Day 8, both as an injection in the deltoid muscle. The injections at Week 5 (Day 36) and Week 9 (Day 64) given in either the deltoid or gluteal muscle and were flexibly dosed (50, 75, 100, or 150 mg eq.). At Week 13 (Day 92) subjects received the same dose of PP1M that was administered at Week 9.	
Reporting group title	Double-Blind: Paliperidone Palmitate 3 month (PP3M) Formulation
Reporting group description: Subjects received Paliperidone Palmitate 3month formulation (PP3M) in a fixed dose of 3.5 fold multiple of the PP1M dose administered at Week 13, that is subjects received fixed dose injections of PP3M (175, 263, 350, or 525 mg eq.) on Week 17, 29, 41, and 53 as injection in deltoid muscle or gluteal muscle. Also the subjects received placebo injection (intralipid) at weeks 21, 25, 33 during the gap period, when they were not receiving PP3M to maintain the blind.	
Reporting group title	Double-Blind: Paliperidone Palmitate 1 month (PP1M) Formulation
Reporting group description: Subjects received Paliperidone Palmitate 1 month formulation (PP1M) in a fixed dose that was administered at Week 9 at every month for 48 weeks, that is, subjects received fixed dose injections of PP1M (50, 75, 100, or 150 mg eq.) as injection on deltoid muscle or gluteal muscle.	

Primary: Percentage Of Subjects Without Relapse At Week 48 During The Double-Blind

End point title	Percentage Of Subjects Without Relapse At Week 48 During The Double-Blind
End point description: Relapse: Psychiatric hospitalization; subjects had an increase of 25 percent in total Positive and Negative Syndrome Scale (PANSS) score from randomization for 2 consecutive assessments separated by 37 days if score at randomization was greater than ($>$) 40; had 10 point increase in total PANSS score from randomization for 2 consecutive assessments separated by 37 days if score at randomization was less than or equal to (\leq) 40; deliberate self injury or exhibited violent behavior resulting in suicide, clinically significant injury; suicidal or homicidal ideation and aggressive behavior; For PANSS items had a score of greater than or equal to (\geq) 5 after randomization for 2 consecutive assessments separated by 37 days on any of above items if maximum score for these above PANSS items was ≤ 3 at randomization; had a score of ≥ 6 after randomization for 2 consecutive assessments separated by 37 days in any above items if maximum score for these above PANSS items was 4 at randomization.	
End point type	Primary
End point timeframe: Up to 48 weeks	

End point values	Double-Blind: Paliperidone Palmitate 3 month (PP3M) Formulation	Double-Blind: Paliperidone Palmitate 1 month (PP1M) Formulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	458	490		
Units: Percentage of Subjects				
number (not applicable)	91.2	90		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: The Kaplan-Meier method was used to estimate the 48-week cumulative estimate of survival (relapse-free). Non-inferiority of PP3M to PP1M was to be concluded if the lower limit of the 2-sided 95% confidence interval of the difference in relapse-free rates between PP3M and PP1M exceeded the pre-specified margin of -15%.	
Comparison groups	Double-Blind:Paliperidone Palmitate 3 month (PP3M) Formulation v Double-Blind:Paliperidone Palmitate 1 month (PP1M) Formulation
Number of subjects included in analysis	948
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference (PP3M-PP1M)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	5.1

Secondary: Change From Double-Blind (DB) Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score at Week 48

End point title	Change From Double-Blind (DB) Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score at Week 48
End point description: The neuropsychiatric symptoms of schizophrenia were assessed by means of the 30 item Positive and Negative Syndrome Scale (PANSS). The PANSS provides a total score (sum of the scores of all 30 items) ranging from 30 to 210, higher scores indicate more severe neuropsychiatric symptoms of schizophrenia. Scores for 3 subscales, that is, for positive subscale (sum of the scores of all 7 items) and negative subscale (sum of the scores of all 7 items) ranges from 7 (absent) to 49 (extreme psychopathology), and for the general psychopathology subscale (sum of the scores of all 16 items) score ranges from 16 (absent) to 112 (extreme psychopathology). The mITT analysis set included all subjects who were randomly assigned to treatment during Double-blind Phase, received at least 1 dose of study drug and did not have any errors in the delivery of active treatment. Here, N=number of subjects analysed is the total subjects who were evaluable for this outcome measure.	
End point type	Secondary
End point timeframe: DB Baseline (Week 17) and 48 week or DB Endpoint	

End point values	Double-Blind:Paliperidone Palmitate 3 month (PP3M) Formulation	Double-Blind:Paliperidone Palmitate 1 month (PP1M) Formulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	481	503		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	57.4 (± 8.56)	58.1 (± 8.88)		
Change from Baseline at DB End point	-3.5 (± 12.5)	-4.3 (± 11.78)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Analysis of covariance (ANCOVA) model with treatment (PP1M, PP3M) and country as factors, and baseline value as a covariate was used. Difference in least squares (LS) means with corresponding 95% CI reported.	
Comparison groups	Double-Blind:Paliperidone Palmitate 3 month (PP3M) Formulation v Double-Blind:Paliperidone Palmitate 1 month (PP1M) Formulation
Number of subjects included in analysis	984
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference of Least Square Means
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	2.34

Secondary: Change From DB Baseline in Clinical Global Impression Severity (CGI-S) Scale Score at Week 48

End point title	Change From DB Baseline in Clinical Global Impression Severity (CGI-S) Scale Score at Week 48
End point description:	
The Clinical Global Impression Severity (CGIS) 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. mITT analysis set included all subjects who were randomly assigned to treatment during Double-blind Phase, received at least 1 dose of study drug and did not have any errors in the delivery of active treatment. Here, N=number of subjects analysed is the total subjects who were evaluable for this outcome measure.	
End point type	Secondary
End point timeframe:	
DB Baseline (Week 17) and 48 week or DB Endpoint	

End point values	Double-Blind:Paliperidone Palmitate 3 month (PP3M) Formulation	Double-Blind:Paliperidone Palmitate 1 month (PP1M) Formulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	481	504		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	2.9 (± 0.57)	2.9 (± 0.66)		
Change from Baseline at DB End point	-0.1 (± 0.84)	-0.1 (± 0.75)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Analysis of covariance (ANCOVA) model with treatment (PP1M, PP3M) and country as factors, and baseline value as a covariate was used. Difference in least squares (LS) means with corresponding 95% CI reported.	
Comparison groups	Double-Blind:Paliperidone Palmitate 3 month (PP3M) Formulation v Double-Blind:Paliperidone Palmitate 1 month (PP1M) Formulation
Number of subjects included in analysis	985
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference of Least Square Means
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.13

Secondary: Change From DB Baseline in Personal and Social Performance (PSP) Total Score at Week 48

End point title	Change From DB Baseline in Personal and Social Performance (PSP) Total Score at Week 48
End point description:	
The Personal and Social Performance (PSP) scale assesses degree of a subject's dysfunction within 4 domains of behavior: socially useful activities, personal and social relationships, selfcare, and disturbing and aggressive behavior. Score ranges from 1 to 100. Subjects with a score of 71 to 100 have mild degree of difficulty; from 31 to 70, varying degrees of disability; less than or equal to 30, functioning so poorly as to require intensive supervision. mITT analysis set included all subjects who were randomly assigned to treatment during Double-blind Phase, received at least 1 dose of study drug and did not have any errors in the delivery of active treatment. Here,N=number of subjects analysed is the total subjects who were evaluable for this outcome measure.	
End point type	Secondary

End point timeframe:

DB Baseline (Week 17) and 48 week or DB Endpoint

End point values	Double-Blind:Paliperidone Palmitate 3 month (PP3M) Formulation	Double-Blind:Paliperidone Palmitate 1 month (PP1M) Formulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	474	495		
Units: Units of a scale				
arithmetic mean (standard deviation)				
Baseline	65.5 (\pm 10.4)	65 (\pm 11.06)		
Change from Baseline at DB End point	1.3 (\pm 10.22)	1.9 (\pm 9.21)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

Analysis of covariance (ANCOVA) model with treatment (PP1M, PP3M) and country as factors, and baseline value as a covariate was used. Difference in least squares (LS) means with corresponding 95% CI reported.

Comparison groups	Double-Blind:Paliperidone Palmitate 3 month (PP3M) Formulation v Double-Blind:Paliperidone Palmitate 1 month (PP1M) Formulation
Number of subjects included in analysis	969
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference of Least Square Means
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.73
upper limit	0.64

Secondary: Percentage Of Subjects Who Met The Criteria for Symptomatic Remission based on Andreasen criteria

End point title	Percentage Of Subjects Who Met The Criteria for Symptomatic Remission based on Andreasen criteria
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End point description:

Symptomatic remission criterion was defined as having a simultaneous score of mild or less on all selected PANSS items (P1, P2, P3, N1, N4, N6, G5, and G9). Symptomatic remission was defined for the last 6 months of the Double-blind Phase as meeting the remission criterion during the 6 months prior to the End of study visit during the Double-blind Phase, with one excursion allowed. mITT analysis set included all subjects who were randomly assigned to treatment during Double-blind Phase, received at least 1 dose of study drug and did not have any errors in the delivery of active treatment. Here, N=number of subjects analysed is the total subjects who were evaluable for this outcome measure.

End point type	Secondary
End point timeframe:	
Weeks 41 to 65	

End point values	Double-Blind:Paliperidone Palmitate 3 month (PP3M) Formulation	Double-Blind:Paliperidone Palmitate 1 month (PP1M) Formulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	483	512		
Units: Percentage of Subjects				
number (not applicable)	58.4	59.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Positive and Negative Syndrome Subscales and Marder Factor Subscale Score at Week 48

End point title	Change From Baseline in Positive and Negative Syndrome Subscales and Marder Factor Subscale Score at Week 48
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End point description:

The neuropsychiatric symptoms of schizophrenia were assessed by means of the 30 item Positive and Negative Syndrome Scale (PANSS). The PANSS provides a total score (sum of the scores of all 30 items) ranging from 30 to 210, higher scores indicate more severe neuropsychiatric symptoms of schizophrenia. Scores for 3 subscales, that is, for positive subscale (sum of the scores of all 7 items) and negative subscale (sum of the scores of all 7 items) ranges from 7 (absent) to 49 (extreme psychopathology), and for the general psychopathology subscale (sum of the scores of all 16 items) score ranges from 16 (absent) to 112 (extreme psychopathology). 5 PANSS Marder factor scores (positive symptoms [range:8 to 56], negative symptoms [range: 7 to 49], disorganized thoughts [range: 7 to 49], uncontrolled hostility/excitement [range: 4 to 28], and anxiety/depression [range: 4 to 28]) were examined to gain insight into the symptoms affected by treatment with the study drug.

End point type	Secondary
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End point timeframe:

DB Baseline (Week 17) and 48 week or DB Endpoint

End point values	Double-Blind:Paliperidone Palmitate 3 month (PP3M) Formulation	Double-Blind:Paliperidone Palmitate 1 month (PP1M) Formulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	483	512		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Positive subscale: Baseline	11.9 (± 3.12)	12 (± 3.19)		
Positive subscale: Change at Endpoint	-0.6 (± 4.31)	-0.9 (± 3.7)		
Negative subscale: Baseline	17.3 (± 4.27)	17.3 (± 4.11)		

Negative subscale: Change at Endpoint	-1.4 (± 3.63)	-1.4 (± 3.67)		
General psychopathology: Baseline	28.2 (± 4.55)	28.8 (± 4.79)		
General psychopathology: Change at Endpoint	-1.4 (± 6.77)	-2 (± 6.57)		
Positive symptoms factor: Baseline	15.7 (± 3.66)	15.8 (± 3.88)		
Positive symptoms factor: Change at Endpoint	-1.1 (± 4.61)	-1.4 (± 4.16)		
Negative symptoms factor: Baseline	16.2 (± 4.03)	16.3 (± 3.9)		
Negative symptoms factor: Change at Endpoint	-1.4 (± 3.57)	-1.3 (± 3.8)		
Disorganized thoughts factor: Baseline	14.2 (± 3.2)	14.3 (± 3.17)		
Disorganized thoughts factor: Change at Endpoint	-1.2 (± 3.36)	-1.2 (± 3.24)		
Uncontrolled hostility Factor: Baseline	5.2 (± 1.64)	5.4 (± 1.77)		
Uncontrolled hostility Factor: Change at Endpoint	0.2 (± 2.31)	-0.2 (± 2.21)		
Anxiety/depression factor: Baseline	6.1 (± 2.02)	6.3 (± 2.12)		
Anxiety/depression factor: Change at Endpoint	0 (± 2.69)	-0.2 (± 2.43)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of informed consent form up to Follow-Up Visit (4 or 12 Weeks after study drug administration)

Adverse event reporting additional description:

For Double-blind (DB) phase, safety analysis set included all subjects who were randomly assigned to treatment during DB Phase and received at least 1 dose of DB study drug. For Open-label Phase, all subjects who received at least 1 dose of open-label study drug and were included in summary of safety assessments for that phase.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Open-Label: Paliperidone Palmitate 1 month (PP1M)
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Reporting group description:

Subjects received Paliperidone Palmitate 1 month formulation (PP1M) in a dose of 150 milligram equivalent (mg eq.) on Day 1 and 100 mg eq. on Day 8, both as an injection in the deltoid muscle. The injections at Week 5 (Day 36) and Week 9 (Day 64) given in either the deltoid or gluteal muscle and were flexibly dosed (50, 75, 100, or 150 mg eq.). At Week 13 (Day 92) subjects received the same dose of PP1M that was administered at Week 9.

Reporting group title	Double-Blind: Paliperidone Palmitate 1 month (PP1M)
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Reporting group description:

Subjects received Paliperidone Palmitate 1 month formulation (PP1M) in a fixed dose that was administered at Week 9 at every month for 48 weeks, that is, subjects received fixed dose injections of PP1M (50, 75, 100, or 150 mg eq.) as injection on deltoid muscle or gluteal muscle.

Reporting group title	Double-Blind: Paliperidone Palmitate 3 month (PP3M) Formulation
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Reporting group description:

Subjects received Paliperidone Palmitate 3month formulation (PP3M) in a fixed dose of 3.5 fold multiple of the PP1M dose administered at Week 13, that is subjects received fixed dose injections of PP3M (175, 263, 350, or 525 mg eq.) on Week 17, 29, 41, and 53 as injection in deltoid muscle or gluteal muscle.

Serious adverse events	Open-Label: Paliperidone Palmitate 1 month (PP1M)	Double-Blind: Paliperidone Palmitate 1 month (PP1M)	Double- Blind: Paliperidone Palmitate 3 month (PP3M) Formulation
Total subjects affected by serious adverse events			
subjects affected / exposed	101 / 1429 (7.07%)	37 / 512 (7.23%)	26 / 504 (5.16%)
number of deaths (all causes)	4	3	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular Carcinoma			
subjects affected / exposed	0 / 1429 (0.00%)	0 / 512 (0.00%)	1 / 504 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Neoplasm Prostate			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (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
Prostate Cancer			
subjects affected / exposed	0 / 1429 (0.00%)	0 / 512 (0.00%)	1 / 504 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (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
Peripheral Artery Thrombosis			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (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
Thrombosis			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (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			
Chest Pain			
subjects affected / exposed	0 / 1429 (0.00%)	1 / 512 (0.20%)	0 / 504 (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
Drug Ineffective			
subjects affected / exposed	2 / 1429 (0.14%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Drug Withdrawal Syndrome			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Menstrual Disorder			
subjects affected / exposed	0 / 1429 (0.00%)	0 / 512 (0.00%)	1 / 504 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (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
Psychiatric disorders			
Acute Psychosis			
subjects affected / exposed	2 / 1429 (0.14%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adjustment Disorder			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (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
Agitation			
subjects affected / exposed	1 / 1429 (0.07%)	1 / 512 (0.20%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol Abuse			

subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (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
Anxiety			
subjects affected / exposed	4 / 1429 (0.28%)	2 / 512 (0.39%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	2 / 4	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety Disorder			
subjects affected / exposed	2 / 1429 (0.14%)	0 / 512 (0.00%)	1 / 504 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delusion			
subjects affected / exposed	4 / 1429 (0.28%)	2 / 512 (0.39%)	1 / 504 (0.20%)
occurrences causally related to treatment / all	1 / 4	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed Mood			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	2 / 1429 (0.14%)	0 / 512 (0.00%)	1 / 504 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	1 / 1429 (0.07%)	1 / 512 (0.20%)	0 / 504 (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
Hallucination, Auditory			
subjects affected / exposed	6 / 1429 (0.42%)	0 / 512 (0.00%)	1 / 504 (0.20%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hostility			

subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomania			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insomnia			
subjects affected / exposed	2 / 1429 (0.14%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Irritability			
subjects affected / exposed	3 / 1429 (0.21%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurosis			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (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
Persecutory Delusion			
subjects affected / exposed	1 / 1429 (0.07%)	1 / 512 (0.20%)	0 / 504 (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
Psychiatric Symptom			
subjects affected / exposed	4 / 1429 (0.28%)	2 / 512 (0.39%)	2 / 504 (0.40%)
occurrences causally related to treatment / all	1 / 5	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic Disorder			
subjects affected / exposed	14 / 1429 (0.98%)	2 / 512 (0.39%)	1 / 504 (0.20%)
occurrences causally related to treatment / all	10 / 15	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Restlessness			

subjects affected / exposed	0 / 1429 (0.00%)	1 / 512 (0.20%)	0 / 504 (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
Schizophrenia			
subjects affected / exposed	31 / 1429 (2.17%)	11 / 512 (2.15%)	12 / 504 (2.38%)
occurrences causally related to treatment / all	17 / 31	2 / 11	2 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia, Paranoid Type			
subjects affected / exposed	0 / 1429 (0.00%)	2 / 512 (0.39%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Self Injurious Behaviour			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (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
Substance-Induced Psychotic Disorder			
subjects affected / exposed	2 / 1429 (0.14%)	1 / 512 (0.20%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal Ideation			
subjects affected / exposed	6 / 1429 (0.42%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide Attempt			
subjects affected / exposed	3 / 1429 (0.21%)	4 / 512 (0.78%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tension			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Alcohol Poisoning			
subjects affected / exposed	0 / 1429 (0.00%)	0 / 512 (0.00%)	1 / 504 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head Injury			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (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
Meniscus Injury			
subjects affected / exposed	0 / 1429 (0.00%)	0 / 512 (0.00%)	1 / 504 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	2 / 1429 (0.14%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to Various Agents			
subjects affected / exposed	1 / 1429 (0.07%)	1 / 512 (0.20%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac disorders			
Cardiac Arrest			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Akathisia			
subjects affected / exposed	4 / 1429 (0.28%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyskinesia			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Somnolence			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stupor			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (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
Syncope			
subjects affected / exposed	0 / 1429 (0.00%)	1 / 512 (0.20%)	0 / 504 (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
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 1429 (0.00%)	1 / 512 (0.20%)	0 / 504 (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
Thrombocytopenia			
subjects affected / exposed	0 / 1429 (0.00%)	0 / 512 (0.00%)	1 / 504 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 1429 (0.00%)	1 / 512 (0.20%)	0 / 504 (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
Gastrointestinal disorders			
Gastrointestinal Disorder			
subjects affected / exposed	0 / 1429 (0.00%)	1 / 512 (0.20%)	0 / 504 (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
Haemorrhoids			

subjects affected / exposed	0 / 1429 (0.00%)	1 / 512 (0.20%)	0 / 504 (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
Pancreatitis Acute			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 1429 (0.14%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus Ureteric			
subjects affected / exposed	0 / 1429 (0.00%)	1 / 512 (0.20%)	0 / 504 (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
Musculoskeletal and connective tissue disorders			
Muscle Rigidity			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 1429 (0.00%)	0 / 512 (0.00%)	1 / 504 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (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
Meningitis Bacterial			
subjects affected / exposed	0 / 1429 (0.00%)	1 / 512 (0.20%)	0 / 504 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Pyelonephritis Acute			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (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
Metabolism and nutrition disorders			
Diabetes Mellitus			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	1 / 504 (0.20%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic Ketoacidosis			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (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
Hyponatraemia			
subjects affected / exposed	1 / 1429 (0.07%)	0 / 512 (0.00%)	0 / 504 (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: 2 %

Non-serious adverse events	Open-Label: Paliperidone Palmitate 1 month (PP1M)	Double-Blind: Paliperidone Palmitate 1 month (PP1M)	Double- Blind: Paliperidone Palmitate 3 month (PP3M)Formulation
Total subjects affected by non-serious adverse events			
subjects affected / exposed	457 / 1429 (31.98%)	208 / 512 (40.63%)	212 / 504 (42.06%)
Investigations			
Weight Decreased			
subjects affected / exposed	10 / 1429 (0.70%)	14 / 512 (2.73%)	14 / 504 (2.78%)
occurrences (all)	10	15	15
Weight Increased			
subjects affected / exposed	64 / 1429 (4.48%)	109 / 512 (21.29%)	105 / 504 (20.83%)
occurrences (all)	64	113	108
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 1429 (0.77%)	7 / 512 (1.37%)	12 / 504 (2.38%)
occurrences (all)	16	7	13

Nervous system disorders			
Akathisia			
subjects affected / exposed	78 / 1429 (5.46%)	14 / 512 (2.73%)	20 / 504 (3.97%)
occurrences (all)	82	18	29
Headache			
subjects affected / exposed	46 / 1429 (3.22%)	26 / 512 (5.08%)	18 / 504 (3.57%)
occurrences (all)	52	30	20
General disorders and administration site conditions			
Injection Site Induration			
subjects affected / exposed	40 / 1429 (2.80%)	6 / 512 (1.17%)	14 / 504 (2.78%)
occurrences (all)	52	6	20
Injection Site Pain			
subjects affected / exposed	127 / 1429 (8.89%)	14 / 512 (2.73%)	12 / 504 (2.38%)
occurrences (all)	178	31	21
Psychiatric disorders			
Anxiety			
subjects affected / exposed	79 / 1429 (5.53%)	22 / 512 (4.30%)	27 / 504 (5.36%)
occurrences (all)	87	58	32
Insomnia			
subjects affected / exposed	94 / 1429 (6.58%)	24 / 512 (4.69%)	16 / 504 (3.17%)
occurrences (all)	109	38	16
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	66 / 1429 (4.62%)	33 / 512 (6.45%)	36 / 504 (7.14%)
occurrences (all)	75	60	45

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2013	The amendment included that additional subjects were added to the planned number of subjects in the Open-label Phase to ensure that there were sufficient number of subjects in the per-protocol analysis set(approximately 380 per arm) and the study was statistically powered as originally planned, after a product manufacturing quality issue due to short syringe plungers was identified with one lot of study drug supply that resulted in some subjects (between 16 and 30 subjects) receiving approximately 75% of the intended dose during the Double-blind Phase; and other minor clarifications were included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported