Clinical trial results:
A Double-blind, Randomized, Active-controlled, Parallel-group Study of Paliperidone Palmitate 6 Month Formulation.

Summary

EudraCT number	2017-001941-28
Trial protocol	DE ES CZ PL IT
Global end of trial date	08 May 2020

Results information

Result version number	v1 (current)
This version publication date	13 May 2021
First version publication date	13 May 2021

Trial information

Trial identification

Sponsor protocol code	R092670PSY3015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03345342
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 US Highway 202, Raritan, NJ, United States, 08869-1420
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	08 May 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The mail objective of the study was to demonstrate that injection cycles consisting of a single administration of paliperidone palmitate 6-month (PP6M) (700 or 1000 milligrams equivalent [mg eq.]) were not less effective than 2 sequentially administered injections of paliperidone palmitate 3-month (PP3M) (350 or 525 mg eq.) for the prevention of relapse in subjects with schizophrenia previously stabilized on corresponding doses of paliperidone palmitate 1-month (PP1M) (100 or 150 mg eq.) or PP3M (350 or 525 mg eq.).

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety evaluations included the assessment of adverse events (AEs), clinical laboratory tests, electrocardiogram (ECG), vital signs, physical examinations, extrapyramidal symptom assessment scales, injection site evaluations and columbia suicide severity rating Scale (C-SSRS) for assessment of suicidal ideation throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 November 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 55
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Brazil: 90
Country: Number of subjects enrolled	Bulgaria: 46
Country: Number of subjects enrolled	Czechia: 45
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	India: 42
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Korea, Republic of: 4
Country: Number of subjects enrolled	Malaysia: 22
Country: Number of subjects enrolled	Mexico: 23

Country: Number of subjects enrolled	Poland: 68
Country: Number of subjects enrolled	Russian Federation: 139
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	Taiwan: 31
Country: Number of subjects enrolled	Turkey: 26
Country: Number of subjects enrolled	Ukraine: 50
Country: Number of subjects enrolled	United States: 125
Worldwide total number of subjects	838
EEA total number of subjects	223

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)	822
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 838 subjects were enrolled either in paliperidone palmitate 1-month (PP1M) or PP3M in Open-label (OL) Phase. Out of 838 subjects, 702 entered the Double-blind (DB) Phase. 702 subjects were randomized in DB Phase (PP6M: n=478; PP3M: n=224), out of which 202 and 416 subjects completed the study in PP3M and PP6M, respectively.

Period 1

Period 1 title	Open-Label Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open Label (OL) PP1M/PP3M (4 Months)

Arm description:

Subjects previously treated with oral antipsychotics, or injectable risperidone, or a moderate or higher dose of PP1M with previous initiation but without previous stabilization (where stabilization was defined as at least 3 months of injections with the last 2 doses being the same strength) received 1 to 5 intramuscular (IM) injections of paliperidone palmitate 1-month (PP1M) 50 to 150 milligrams equivalent (mg eq.) to achieve stability during Open-label (OL) transition phase and to initiate the OL maintenance phase. Subjects received single dose of IM injections of PP1M as 100 or 150 mg eq. or paliperidone palmitate 3-month (PP3M) as 350 or 525 mg eq was administered during the OL-maintenance Phase. Open-label phase duration was of 4 Months (OL-transition of 1 month and OL-maintenance of 3 months).

Arm type	Experimental
Investigational medicinal product name	PP3M (350 or 525 mg eq.)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects were administered single dose of PP3M (350 or 525 mg eq.) injection for 3-month during the OL-maintenance Phase.

Investigational medicinal product name	PP1M (50 or 150 mg eq.)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects were administered single dose of PP1M (50 or 150 mg eq.) injection for 1-month during the OL-transition Phase.

Number of subjects in period 1	Open Label (OL) PP1M/PP3M (4 Months)
Started	838
Completed	702
Not completed	136
Adverse event, serious fatal	1
Physician decision	4
Consent withdrawn by subject	57
Adverse event, non-fatal	30
Initiated prohibited medication	2
Other	15
Non-compliance with study drug	4
Lost to follow-up	9
Lack of efficacy	6
Protocol deviation	8

Period 2

Period 2 title	Double Blind Phase (12 Months)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Carer

Arms

Are arms mutually exclusive?	No
Arm title	Double-blind (DB) PP3M

Arm description:

Subjects received four doses of PP3M (350 or 525 mg eq.) IM injection for up to 12 months (one dose every 3 month) during DB phase.

Arm type	Active comparator
Investigational medicinal product name	PP3M
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects were administered single dose of PP3M (350 or 525 mg eq.) injection every 3-month for up to 12 months during the DB Phase.

Arm title	Double-blind (DB) PP6M

Arm description:

Subjects received two doses of PP6M (700 or 1000 mg eq.) IM injection for 12 months (one dose every 6 months), during the DB Phase. To maintain blinding, subjects who were assigned to treatment with PP6M in this arm, received IM injections of matching placebo at the 3-month time points between their 6-month doses of PP6M drug.

Arm type	Experimental
Investigational medicinal product name	PP6M
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects were administered two doses of PP6M (700 or 1000 mg eq.) injection every 6-months for up to 12 Months during the DB Phase.

Number of subjects in period 2	Double-blind (DB) PP3M	Double-blind (DB) PP6M
Started	224	478
Completed	202	416
Not completed	22	62
Adverse event, serious fatal	2	1
Physician decision	1	4
Consent withdrawn by subject	16	38
Adverse event, non-fatal	1	6
Initiated prohibited medication	-	2
Other	1	3
Lost to follow-up	1	7
Protocol deviation	-	1

Period 3

Period 3 title	Follow-up Phase (12 Months)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	No
Arm title	Follow-up (FU) Phase PP3M

Arm description:

Subjects who have received at least 1 dose of PP3M (350 or 525 mg eq.) IM injection during double-blind phase but then have relapsed or have met other relevant conditions for withdrawal or discontinuation can participate in the Follow-up phase PP3M (350 or 525 mg eq.) IM injection for up to 12 months for evaluating efficacy and safety.

Arm type	Active comparator

Investigational medicinal product name	PP3M
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects who received PP3M (350 or 525 mg eq.) IM injection during DB-phase were followed-up to 12 months during FU phase.

Arm title	Follow-up (FU) Phase PP6M

Arm description:

Subjects who received PP6M (700 or 1000 mg eq.) IM injection for up to 12 months for evaluating efficacy and safety

Arm type	Experimental
Investigational medicinal product name	PP6M
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects who received two doses of PP6M (700 or 1000 mg eq.) IM injection during DB-phase were followed-up to 12 months during FU phase.

Number of subjects in period 3	Follow-up (FU) Phase PP3M	Follow-up (FU) Phase PP6M
Started	42	109
Completed	34	78
Not completed	8	31
Consent withdrawn by subject	5	15
Physician decision	-	5
Adverse event, non-fatal	-	4
Other	3	1
Lost to follow-up	-	6

Baseline characteristics

Reporting groups	
Reporting group title	Open Label (OL) PP1M/PP3M (4 Months)

Reporting group description:

Subjects previously treated with oral antipsychotics, or injectable risperidone, or a moderate or higher dose of PP1M with previous initiation but without previous stabilization (where stabilization was defined as at least 3 months of injections with the last 2 doses being the same strength) received 1 to 5 intramuscular (IM) injections of paliperidone palmitate 1-month (PP1M) 50 to 150 milligrams equivalent (mg eq.) to achieve stability during Open-label (OL) transition phase and to initiate the OL maintenance phase. Subjects received single dose of IM injections of PP1M as 100 or 150 mg eq. or paliperidone palmitate 3-month (PP3M) as 350 or 525 mg eq was administered during the OL-maintenance Phase. Open-label phase duration was of 4 Months (OL-transition of 1 month and OL-maintenance of 3 months).

Reporting group values	Open Label (OL) PP1M/PP3M (4 Months)	Total	
Number of subjects	838	838	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	822	822	
From 65 to 84 years	16	16	
85 years and over	0	0	
Title for AgeContinuous Units: years			
arithmetic mean	40.8		
standard deviation	± 11.68	-	
Title for Gender Units: subjects			
Female	285	285	
Male	553	553	

End points

End points reporting groups

Reporting group title	Open Label (OL) PP1M/PP3M (4 Months)

Reporting group description:

Subjects previously treated with oral antipsychotics, or injectable risperidone, or a moderate or higher dose of PP1M with previous initiation but without previous stabilization (where stabilization was defined as at least 3 months of injections with the last 2 doses being the same strength) received 1 to 5 intramuscular (IM) injections of paliperidone palmitate 1-month (PP1M) 50 to 150 milligrams equivalent (mg eq.) to achieve stability during Open-label (OL) transition phase and to initiate the OL maintenance phase. Subjects received single dose of IM injections of PP1M as 100 or 150 mg eq. or paliperidone palmitate 3-month (PP3M) as 350 or 525 mg eq was administered during the OL-maintenance Phase. Open-label phase duration was of 4 Months (OL-transition of 1 month and OL-maintenance of 3 months).

Reporting group title	Double-blind (DB) PP3M

Reporting group description:

Subjects received four doses of PP3M (350 or 525 mg eq.) IM injection for up to 12 months (one dose every 3 month) during DB phase.

Reporting group title	Double-blind (DB) PP6M

Reporting group description:

Subjects received two doses of PP6M (700 or 1000 mg eq.) IM injection for 12 months (one dose every 6 months), during the DB Phase. To maintain blinding, subjects who were assigned to treatment with PP6M in this arm, received IM injections of matching placebo at the 3-month time points between their 6-month doses of PP6M drug.

Reporting group title	Follow-up (FU) Phase PP3M

Reporting group description:

Subjects who have received at least 1 dose of PP3M (350 or 525 mg eq.) IM injection during double-blind phase but then have relapsed or have met other relevant conditions for withdrawal or discontinuation can participate in the Follow-up phase PP3M (350 or 525 mg eq.) IM injection for up to 12 months for evaluating efficacy and safety.

Reporting group title	Follow-up (FU) Phase PP6M

Reporting group description:

Subjects who received PP6M (700 or 1000 mg eq.) IM injection for up to 12 months for evaluating efficacy and safety

Primary: Time to Relapse During the Double-Blind (DB) Phase

End point title	Time to Relapse During the Double-Blind (DB) Phase

End point description:

Relapse: a) Psychiatric hospitalization; b) Positive and Negative Syndrome Scale (PANSS) total score: Increase of 25%,10point increase in PANSS for 2 analysis separated by 3-7 days if score was greater than (>) 40, less than equal to (=<)40 ; c) Subject inflicted knowing self-injury/shown violent behavior leading to suicide, clinically significant injury to him/herself or other person/property; d)Subject had suicidal/homicidal ideation/violent behavior that was clinically significant as per investigator; e) PANSS items P1- delusions,P2- conceptual disorganization, P3-hallucinatory behavior, P6- suspiciousness/ persecution, P7-hostility, G8-uncooperativeness: score: =>5, =>6 for 2 analysis separated by 3-7 days on any items if maximum score for PANSS:=<3 or 4, respectively. DB Intent-to-Treat (ITT) Analysis Set included subjects who were randomly assigned to PP6M/PP3M during DB Phase, received at least 1 dose of DB drug. Here,99999 refers that data is not collected for referred arm.

End point type	Primary

End point timeframe:

At Month 12 of DB Phase (Up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	478		
Units: Days				
median (confidence interval 95%)	99999 (-99999 to +99999)	99999 (-99999 to +99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-blind (DB) PP6M v Double-blind (DB) PP3M
Number of subjects included in analysis	702
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean Percentage Difference
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	1.1

Secondary: Changes From Baseline in the PANSS Total Score

End point title	Changes From Baseline in the PANSS Total Score

End point description:

The neuropsychiatric symptoms of schizophrenia were assessed using the 30-item PANSS scale, which provides a total score (sum of the scores for all 30 items) and scores for 3 subscales: the 7-item positive-symptom (P) subscale, the 7-item negative-symptom (N) subscale, and the 16-item general-psychopathology symptom (G) subscale. Each item is rated on a scale from 1 (absent) to 7 (extreme). The PANSS total score ranging from 30 (absent disease)-210 (more severe neuropsychiatric symptoms of schizophrenia). DB ITT Analysis Set included all subjects who were randomly assigned to treatment group of either PP6M or PP3M during the DB Phase and received at least 1 dose of DB study drug. Here 'N' (number of subjects analyzed), included all subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (DB) to 12 Months of DB Phase (Up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	473		
Units: Units on a scale				
arithmetic mean (standard deviation)	-1.6 (± 7.40)	-1.8 (± 8.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in the Clinical Global Impression – Severity (CGI-S) Total Score up to 12 Months of the DB Phase

End point title	Changes From Baseline in the Clinical Global Impression – Severity (CGI-S) Total Score up to 12 Months of the DB Phase

End point description:

The CGI-S total score is clinician rated and measures the clinical global impressions of severity of the subject's psychosis on a 7-point scale, from "Not ill" to "Extremely Severe". DB ITT Analysis Set included all subjects who were randomly assigned to treatment group of either PP6M or PP3M during the DB Phase and received at least 1 dose of DB study drug. Here 'N' (number of subjects analyzed), included all subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (DB) to 12 Months of DB Phase (Up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	475		
Units: Units on a scale				
arithmetic mean (standard deviation)	0.0 (± 0.63)	0.0 (± 0.70)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in the Personal and Social Performance (PSP) Scale Total Score up to 12 Months of the DB Phase

End point title	Changes From Baseline in the Personal and Social Performance (PSP) Scale Total Score up to 12 Months of the DB Phase

End point description:

The PSP scale assesses the degree of dysfunction a subject exhibits within 4 domains of behavior: (a) socially useful activities, (b) personal and social relationships, (c) self-care, and (d) disturbing and aggressive behavior. The results of the assessment are converted to a numerical score from 1 to 100 points, functioning (91 to 100 points), good functioning (81 to 90 points), mild difficulties (71 to 80 points), etc, as shown in the Manual of Assessments. Scores from 31 to 70 points indicate varying degrees of difficulty, and scores below 30 points indicate functioning so poor that intensive support or supervision is needed. DB ITT Analysis Set included all subjects who were randomly assigned to treatment group of either PP6M or PP3M during the DB Phase and received at least 1 dose of DB study drug. Here 'N' (number of subjects analyzed), included all subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (DB) to 12 Months of DB Phase (Up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	473		
Units: Units on a scale				
arithmetic mean (standard deviation)	1.1 (± 8.11)	1.0 (± 7.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Symptomatic Remission (SR) During the Double-Blind Phase (PANSS Total Score)

End point title	Number of Subjects with Symptomatic Remission (SR) During the Double-Blind Phase (PANSS Total Score)

End point description:

Achieving Remission: For single observations, transitory SE defined as simultaneous score of mild/less (≤3 points) on PANSS items: positive items P1,P2,P3; negative items N1 (blunted affect), N4 (social withdrawal), N6 (lack of spontaneity); general-psychopathology items G5 (mannerisms/ posturing),G9 (unusual thought content). For multiple observations, durable symptomatic remission is defined as meeting those remission criteria for a 6-month period. DB ITT included all subjects who were randomly assigned to treatment group of either PP6M or PP3M, received at least 1 dose of DB study drug.

End point type	Secondary

End point timeframe:

12 months of DB-phase (up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	478		
Units: Subjects				
number (not applicable)	157	317		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Satisfaction With Participants in Social Roles (SPSR) Total Score

End point title	Change From Baseline in the Satisfaction With Participants in Social Roles (SPSR) Total Score

End point description:

The Patient-Reported Outcomes Measurement Information System (PROMIS) group developed and evaluated the Satisfaction With Participation in Social Roles (SPSR) with funding from the US National Institutes of Health (NIH) and other academic and research grants. The SPSR asked subjects to consider the past 7 days and to rate 8 items on 5-point Likert scales, with higher scores representing higher satisfaction. DB ITT Analysis Set included all subjects who were randomly assigned to treatment group of either PP6M or PP3M during the DB Phase and received at least 1 dose of DB study drug. Here 'N' (number of subjects analyzed), included all subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (DB) to 12 Months of DB Phase (Up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	154		
Units: Units on a scale				
arithmetic mean (standard deviation)	0.9 (± 7.15)	0.6 (± 6.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in the Treatment Satisfaction Questionnaire for Medication (TSQM-9) Score

End point title	Changes From Baseline in the Treatment Satisfaction Questionnaire for Medication (TSQM-9) Score

End point description:

The 9-item abbreviated treatment satisfaction questionnaire for medication (TSQM-9) was found to be a reliable and valid measure to assess treatment satisfaction in naturalistic study designs.5 Items are scored on 5- or 7-point Likert scales, with higher scores representing higher satisfaction. Subjects are asked to consider the time frame of the last 2 to 3 weeks, or since the last time the medication was used. DB ITT Analysis Set included all subjects who were randomly assigned to treatment group of either PP6M or PP3M during the DB Phase and received at least 1 dose of DB study drug. Here 'N' (number of subjects analyzed), included all subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (DB) to 12 Months of DB Phase (Up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	279		
Units: Units on a scale				
arithmetic mean (standard deviation)	2.5 (± 19.29)	0.5 (± 20.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in the Simpson-Angus Rating Scale (SAS) Total Score

End point title	Changes From Baseline in the Simpson-Angus Rating Scale (SAS) Total Score

End point description:

The SAS rates 10 items for general extrapyramidal symptoms (EPS) on a 5-point scale from 0 (normal) to 4 (extreme), including gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head rotation, Glabellar tap, tremor, and salivation. The SAS global score is the average score (total sum of item scores divided by the number of items) and ranges between 0 and 4. Negative change in score indicates improvement. Higher scores denote more severe condition of EPS. DB ITT Analysis Set included all subjects who were randomly assigned to treatment group of either PP6M or PP3M during the DB Phase and received at least 1 dose of DB study drug. Here 'N' (number of subjects analyzed), included all subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (DB) to 12 Months of DB Phase (Up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	477		
Units: Units on a scale				
median (full range (min-max))	0.00 (-0.6 to 2.1)	0.00 (-0.6 to 1.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Symptoms of Akathisia Assesses Using Barnes Akathisia Rating Scale (BARS) Score

End point title	Number of Subjects With Symptoms of Akathisia Assesses Using Barnes Akathisia Rating Scale (BARS) Score

End point description:

The BARS assesses akathisia via 1 objective rating and 2 subjective ratings (awareness of restlessness and reported distress related to restlessness); each is scored from 0 to 3 points. It also assesses akathisia via 1 global clinical rating scored from 0 to 5 points. For all items, anchors are provided for each value and higher scores indicate worse akathisia. DB ITT Analysis Set included all subjects who were randomly assigned to treatment group of either PP6M or PP3M during the DB Phase and received at least 1 dose of DB study drug. Here 'N' (number of subjects analyzed), included all subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (DB) to 12 Months of DB Phase (Up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	477		
Units: Subjects				
Absent	212	451		
Questionable	7	19		
Mild Akathisia	2	6		
Moderate Akathisia	0	1		
Marked Akathisia	0	0		
Severe Akathisia	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Abnormal Involuntary Movement Scale (AIMS) Total Score

End point title	Change From Baseline in the Abnormal Involuntary Movement Scale (AIMS) Total Score

End point description:

Dyskinesia was assessed using the AIMS. The AIMS is included in the Early Clinical Development Evaluation Unit Assessment Manual from the United States National Institute of Mental Health (NIMH). The AIMS rates 9 items about dyskinesia on scale as 0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe. It rates 1 item about the subject's awareness of abnormal movements as 0 = no awareness; 1 = aware, no distress; 2 = aware, mild distress; 3 = aware, moderate distress; and 4 = aware, severe distress. It has 2 yes/no questions about dental status. Negative change in score indicates improvement. DB ITT Analysis Set included all subjects who were randomly assigned to treatment group of either PP6M or PP3M during the DB Phase and received at least 1 dose of DB study drug. Here 'N' (number of subjects analyzed), included all subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (DB) to 12 Months of DB Phase (Up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	477		
Units: Units on a scale				
median (full range (min-max))	0.0 (-3 to 2)	0.0 (-7 to 14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Based on Columbia Suicide Severity Rating Scale (C-SSRS) Total Score

End point title	Number of Subjects Based on Columbia Suicide Severity Rating Scale (C-SSRS) Total Score

End point description:

The C-SSRS is a clinical interview which provides a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. It can also be used during treatment to monitor for clinical worsening. The C-SSRS Baseline Version assesses suicidal behavior and ideation over a lifetime, and the C-SSRS "since last visit" version assesses those parameters over an interval. DB ITT Analysis Set included all subjects who were randomly assigned to treatment group of either PP6M or PP3M during the DB Phase and received at least 1 dose of DB study drug.

End point type	Secondary

End point timeframe:

Baseline (DB) to endpoint (12 Months of DB Phase [Up to 16 months])

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	478		
Units: Subjects				
Baseline (0 No event)	221	477		
Baseline (1 Wish to be dead)	3	0		
Baseline (2 Non-specific suicidal thought)	0	1		
Baseline (3 Suicidal ideation-no intent)	0	0		
Baseline (4 Ideation with intent, no plan)	0	0		
Baseline (5 Ideation with plan/intent)	0	0		
Baseline (6 Preparatory acts/behavior)	0	0		
Baseline (7 Aborted attempt)	0	0		
Baseline (8 Interrupted attempt)	0	0		
Baseline (9 Actual attempt)	0	0		
End Point (0 No event)	218	471		
End Point (1 Wish to be dead)	1	1		
End Point (2 Non-specific suicidal thought)	0	0		
End Point (3 Suicidal ideation-no intent)	0	1		
End Point (4 Ideation with intent, no plan)	1	0		
End Point (5 Ideation with plan/intent)	1	2		
End Point (6 Preparatory acts/behavior)	0	0		

End Point (7 Aborted attempt)	0	0		
End Point (8 Interrupted attempt)	0	0		
End Point (9 Actual attempt)	0	1		
End Point (10 Suicide)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Abnormal Electrocardiogram (ECG) Values During DB Phase

End point title	Number of Subjects With Treatment-emergent Abnormal Electrocardiogram (ECG) Values During DB Phase

End point description:

Number of subjects with clinically significant abnormalities in ECG measurements were reported. Double-blind Safety analysis set (DB Safety) includes all subjects who were randomly assigned to treatment group of either PP6M or PP3M during the Double-blind Phase and received at least 1 dose of DB study drug. Here 'N' (number of subjects analyzed), included all subjects who were evaluable for this endpoint. Less than equal to (=<) and greater than equal to (>=).

End point type	Secondary

End point timeframe:

Baseline (DB) to 12 Months of DB Phase (Up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	474		
Units: Subjects				
Heart Rate value =<50	5	9		
Heart Rate value =>100	20	36		
PR Duration value >= 210	3	8		
QRS Duration value =< 50	0	0		
QRS Duration value => 120	1	2		
QT Duration value =< 200	0	0		
QT Duration value => 500	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Body Weight During DB Phase

End point title	Change From Baseline in the Body Weight During DB Phase

End point description:

Change from baseline in body weight was reported. DB ITT Analysis Set included all subjects who were randomly assigned to treatment group of either PP6M or PP3M during the DB Phase and received at least 1 dose of DB study drug. Here 'N' (number of subjects analyzed), included all subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (DB) to 12 Months of DB Phase (Up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	473		
Units: Kilogram per meter^2 (kg/m^2)				
arithmetic mean (standard deviation)	0.3 (± 1.78)	0.0 (± 1.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Waist Circumference During DB Phase

End point title	Change From Baseline in the Waist Circumference During DB Phase

End point description:

Change from baseline in Weight Circumference was reported. DB ITT Analysis Set included all subjects who were randomly assigned to treatment group of either PP6M or PP3M during the DB Phase and received at least 1 dose of DB study drug. Here 'N' (number of subjects analyzed), included all subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (DB) to 12 Months of DB Phase (Up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	473		
Units: Centimeter (cm)				
arithmetic mean (standard deviation)	0.82 (± 5.137)	0.37 (± 5.157)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Weight During DB Phase

End point title	Change From Baseline in the Weight During DB Phase

End point description:

Change from baseline in weight was reported. DB ITT Analysis Set included all subjects who were randomly assigned to treatment group of either PP6M or PP3M during the DB Phase and received at

least 1 dose of DB study drug. Here 'N' (number of subjects analyzed), included all subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (DB) to 12 Months of DB Phase (Up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	473		
Units: Kilogram (kg)				
arithmetic mean (standard deviation)	0.96 (± 5.103)	0.10 (± 4.959)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Vital Signs (Pulse Rate) During DB Phase

End point title	Change From Baseline in the Vital Signs (Pulse Rate) During DB Phase

End point description:

Change from baseline vital signs (pulse rate) were reported. DB ITT Analysis Set included all subjects who were randomly assigned to treatment group of either PP6M or PP3M during the DB Phase and received at least 1 dose of DB study drug. Here 'N' (number of subjects analyzed), included all subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (DB) to 12 Months of DB Phase (Up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	473		
Units: beats/minute				
arithmetic mean (standard deviation)				
Supine Pulse Rate	1.2 (± 11.57)	0.6 (± 11.56)		
Standing Pulse Rate	2.6 (± 12.28)	0.9 (± 12.60)		
Pulse Rate(Standing-Supine)	1.5 (± 8.85)	0.2 (± 8.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Vital Signs (Systolic Blood pressure [SBP] and Diastolic Blood Pressure [DBP]) During DB Phase

End point title	Change From Baseline in the Vital Signs (Systolic Blood pressure [SBP] and Diastolic Blood Pressure [DBP]) During DB Phase

End point description:

Change from baseline vital signs including SBP and DBP (supine/standing) were reported. DB ITT Analysis Set included all subjects who were randomly assigned to treatment group of either PP6M or PP3M during the DB Phase and received at least 1 dose of DB study drug. Here 'N' (number of subjects analyzed), included all subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (DB) to 12 Months of DB Phase (Up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	473		
Units: Millimetre of mercury (mmHg)				
arithmetic mean (standard deviation)				
Supine SBP	-0.3 (± 13.14)	0.6 (± 9.96)		
Standing SBP	0.8 (± 12.08)	1.3 (± 10.40)		
SBP (Standing-Supine)	1.0 (± 9.83)	0.6 (± 7.32)		
Supine DBP	0.1 (± 9.25)	-0.4 (± 7.49)		
Standing DBP	0.3 (± 9.39)	0.4 (± 7.48)		
DBP (Standing-Supine)	0.2 (± 7.79)	0.7 (± 6.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Positive and Negative Syndrome Scale (PANSS) Subscales During DB Phase

End point title	Change From Baseline Positive and Negative Syndrome Scale (PANSS) Subscales During DB Phase

End point description:

The neuropsychiatric symptoms of schizophrenia were assessed using the 30-item PANSS scale, which provides a total score (sum of the scores for all 30 items) and scores for 3 subscales: the 7-item positive-symptom (P) subscale, the 7-item negative-symptom (N) subscale, and the 16-item general-psychopathology symptom (G) subscale. Each item was rated on a scale from 1 (absent) to 7 (extreme). DB ITT Analysis Set included all subjects who were randomly assigned to treatment group of either PP6M or PP3M during the DB Phase and received at least 1 dose of DB study drug. Here 'N' (number of subjects analyzed), included all subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (DB) to 12 Months of DB Phase (Up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	473		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Positive Subscale Score	-0.1 (± 2.82)	-0.1 (± 3.30)		
Negative Subscale Score	-0.6 (± 2.61)	-0.7 (± 2.70)		
General Psychopathology Subscale Score	-0.9 (± 4.18)	-1.0 (± 4.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Clinically Significant Abnormal Laboratory Values in Chemistry During DB Phase

End point title	Number of Subjects With Treatment-Emergent Clinically Significant Abnormal Laboratory Values in Chemistry During DB Phase

End point description:

Number of subjects with clinically significant abnormal laboratory values in chemistry included alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bicarbonate, bilirubin, calcium, chloride, cholesterol, creatinine, gamma glutamyl transferase (GGT), glucose, high-density lipoproteins (HDL) cholesterol, low density lipoproteins (LDL) cholesterol, lactate dehydrogenase,phosphate, potassium, protein, sodium, triglycerides, urate, urea nitrogen were reported. Double-Blind Safety analysis set (DB Safety) includes all subjects who were randomly assigned to treatment group of either PP6M or PP3M during the Double-blind Phase and received at least 1 dose of DB study drug. Here 'N' (number of subjects analyzed), included all subjects who were evaluable for this endpoint. Here 'n' (number analyzed) included all evaluable subjects who were analyzed at specified categories. Abnormally Low (ABL) and Abnormally High (ABH).

End point type	Secondary

End point timeframe:

Up to 12 Months of DB Phase (Up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	464		
Units: Subjects				
Alanine Aminotransferase (U/L) ABH (n= 216, 464)	0	1		
Albumin (g/L) ABL (n= 216, 464)	0	0		
Albumin (g/L) ABH (n= 216, 464)	0	0		
Alkaline Phosphatase (U/L) ABH (n= 216, 464)	0	0		
Aspartate Aminotransferase (U/L) ABH (n= 216, 464)	0	0		
Bicarbonate (mmol/L) ABL (n= 216, 461)	0	3		
Bicarbonate (mmol/L) ABH (n= 216, 461)	0	0		

Bilirubin (umol/L) ABH (n= 208, 447)	0	1		
Calcium (mmol/L) ABL (n= 216, 464)	0	0		
Calcium (mmol/L) ABH (n= 216, 464)	0	0		
Chloride (mmol/L) ABL (n= 216, 463)	4	5		
Chloride (mmol/L) ABH (n= 216, 463)	0	0		
Cholesterol (mmol/L) ABH (n= 216, 463)	2	4		
Creatinine (umol/L) ABH (n= 216, 464)	0	0		
Gamma Glutamyl Transferase (U/L) ABH (n= 216, 464)	0	2		
Glucose (mmol/L) ABL (n= 216, 464)	1	0		
Glucose (mmol/L) ABH (n= 216, 464)	1	5		
HDL Cholesterol (mmol/L) ABL (n= 216, 463)	18	40		
LDL Cholesterol (mmol/L) ABL (n= 216, 463)	33	44		
LDL Cholesterol (mmol/L) ABH (n= 216, 463)	9	22		
Lactate Dehydrogenase (U/L) ABH (n= 215, 456)	0	1		
Phosphate (mmol/L) ABL (n= 216, 464)	1	8		
Phosphate (mmol/L) ABH (n= 216, 464)	0	0		
Potassium (mmol/L) ABL (n= 216, 463)	0	0		
Potassium (mmol/L) ABH (n= 216, 463)	0	0		
Protein (g/L) ABL (n= 216, 464)	0	1		
Sodium (mmol/L) ABL (n= 216, 463)	1	0		
Sodium (mmol/L) ABH (n= 216, 463)	0	0		
Triglycerides (mmol/L) ABH (n= 216, 463)	4	6		
Urate (umol/L) ABL (n= 215, 463)	0	0		
Urate (umol/L) ABH (n= 215, 463)	1	4		
Urea Nitrogen (mmol/L) ABH (n= 215, 464)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Clinically Significant Abnormal Laboratory Values in Hematology During DB Phase

End point title	Number of Subjects With Treatment-Emergent Clinically Significant Abnormal Laboratory Values in Hematology During DB Phase

End point description:

Number of subjects with clinically significant abnormal laboratory values in hematology included hemoglobin (Hb), hematocrit (Hct), red blood cell (RBC) count, white blood cell (WBC) count with differential, platelets, hemoglobin A1c. Double-blind Safety analysis set (DB Safety) includes all subjects who were randomly assigned to treatment group of either PP6M or PP3M during the Double-blind Phase and received at least 1 dose of DB study drug. Here 'N' (number of subjects analyzed), included all subjects who were evaluable for this endpoint. Here 'n' (number analyzed) included all evaluable subjects who were analyzed at specified categories. Abnormally Low (ABL) and Abnormally High (ABH).

End point type	Secondary

End point timeframe:
Up to 12 Months of DB Phase (Up to 16 months)

End point values	Double-blind (DB) PP3M	Double-blind (DB) PP6M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215	459		
Units: Subjects				
Basophils ABL (n=215,459)	0	0		
Eosinophils ABL (n=215,459)	1	1		
Erythrocytes ABL (n=215,459)	1	0		
Erythrocytes ABH (n=215,459)	0	0		
Hematocrit ABL (n=215,457)	0	1		
Hematocrit ABH (n=215,457)	0	0		
Hemoglobin (g/L) ABL (n=215,459)	1	0		
Hemoglobin (g/L) ABH (n=215,459)	0	0		
Leukocytes ABL (n=215,459)	0	0		
Leukocytes ABH (n=215,459)	2	4		
Lymphocytes ABL (n=215,459)	0	2		
Lymphocytes ABH (n=215,459)	1	1		
Monocytes ABH (n=215,459)	0	0		
Neutrophils ABL (n=215,459)	1	0		
Neutrophils ABH (n=215,459)	0	0		
Platelets ABL (n=214,458)	0	0		
Platelets ABH (n=214,458)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 2.5 Years

Adverse event reporting additional description:

OL Safety set included all subjects who received at least 1 dose of OL study drug (excluding the first study subjects if re-screened), both transition and maintenance phases. DB Safety set included all subjects who were randomly assigned to treatment group either PP6M or PP3M during DB Phase and received at least 1 dose of DB study drug.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Open Label (OL) PP1M/PP3M (4 Months)

Reporting group description:

Subjects previously treated with oral antipsychotics, or injectable risperidone, or a moderate or higher dose of PP1M with previous initiation but without previous stabilization (where stabilization was defined as at least 3 months of injections with the last 2 doses being the same strength) received 1 to 5 intramuscular (IM) injections of paliperidone palmitate 1-month (PP1M) 50 to 150 milligrams equivalent (mg eq.) to achieve stability during Open-label (OL) transition phase and to initiate the OL maintenance phase. Subjects received single dose of IM injections of PP1M as 100 or 150 mg eq. or paliperidone palmitate 3-month (PP3M) as 350 or 525 mg eq was administered during the OL-maintenance Phase. Open-label phase duration was of 4 Months (OL-transition of 1 month and OL-maintenance of 3 months).

Reporting group title	Double-blind (DB) Phase PP3M

Reporting group description:

Subjects received four doses of PP3M (350 or 525 mg eq.) IM injection for up to 12 months (one dose every 3 month) during DB phase.

Reporting group title	Double-blind (DB) Phase PP6M

Reporting group description:

Subjects received two doses of PP6M (700 or 1000 mg eq.) IM injection for 12 months (one dose every 6 months), during the DB Phase. To maintain blinding, subjects who were assigned to treatment with PP6M in this arm, received IM injections of matching placebo at the 3-month time points between their 6-month doses of PP6M drug.

Reporting group title	Follow-up (FU) Phase PP3M

Reporting group description:

Subjects who have received at least 1 dose of PP3M (350 or 525 mg eq.) IM injection during double-blind phase but then have relapsed or have met other relevant conditions for withdrawal or discontinuation can participate in the Follow-up phase PP3M (350 or 525 mg eq.) IM injection for up to 12 months for evaluating efficacy and safety.

Reporting group title	Follow-up (FU) Phase PP6M

Reporting group description:

Subjects who received PP6M (700 or 1000 mg eq.) IM injection for up to 12 months for evaluating efficacy and safety

Serious adverse events	Open Label (OL) PP1M/PP3M (4 Months)	Double-blind (DB) Phase PP3M	Double-blind (DB) Phase PP6M
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 838 (2.74%)	15 / 224 (6.70%)	24 / 478 (5.02%)
number of deaths (all causes)	1	2	1

number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain Neoplasm			
subjects affected / exposed	0 / 838 (0.00%)	0 / 224 (0.00%)	0 / 478 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Lymphocytic Leukaemia			
subjects affected / exposed	0 / 838 (0.00%)	1 / 224 (0.45%)	0 / 478 (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
Nasal Sinus Cancer			
subjects affected / exposed	0 / 838 (0.00%)	0 / 224 (0.00%)	0 / 478 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm Malignant			
subjects affected / exposed	0 / 838 (0.00%)	0 / 224 (0.00%)	1 / 478 (0.21%)
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			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 838 (0.00%)	0 / 224 (0.00%)	1 / 478 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Artery Occlusion			
subjects affected / exposed	0 / 838 (0.00%)	1 / 224 (0.45%)	0 / 478 (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
Surgical and medical procedures			
Mammoplasty			
subjects affected / exposed	0 / 838 (0.00%)	1 / 224 (0.45%)	0 / 478 (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
Pregnancy, puerperium and perinatal conditions			

Abortion Spontaneous			
subjects affected / exposed	0 / 838 (0.00%)	0 / 224 (0.00%)	1 / 478 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 838 (0.00%)	0 / 224 (0.00%)	1 / 478 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sudden Death			
subjects affected / exposed	0 / 838 (0.00%)	1 / 224 (0.45%)	0 / 478 (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
Reproductive system and breast disorders			
Priapism			
subjects affected / exposed	0 / 838 (0.00%)	0 / 224 (0.00%)	1 / 478 (0.21%)
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			
Acute Respiratory Failure			
subjects affected / exposed	0 / 838 (0.00%)	1 / 224 (0.45%)	0 / 478 (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
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	2 / 838 (0.24%)	1 / 224 (0.45%)	0 / 478 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 838 (0.12%)	0 / 224 (0.00%)	1 / 478 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			

subjects affected / exposed	0 / 838 (0.00%)	1 / 224 (0.45%)	0 / 478 (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
Psychiatric disorders			
Acute Psychosis			
subjects affected / exposed	1 / 838 (0.12%)	0 / 224 (0.00%)	0 / 478 (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
Adjustment Disorder with Mixed Anxiety and Depressed Mood			
subjects affected / exposed	0 / 838 (0.00%)	0 / 224 (0.00%)	1 / 478 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adjustment Disorder with Mixed Disturbance of Emotion and Conduct			
subjects affected / exposed	0 / 838 (0.00%)	1 / 224 (0.45%)	0 / 478 (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
Alcohol Withdrawal Syndrome			
subjects affected / exposed	1 / 838 (0.12%)	0 / 224 (0.00%)	0 / 478 (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
Behavioural Addiction			
subjects affected / exposed	1 / 838 (0.12%)	0 / 224 (0.00%)	0 / 478 (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
Completed Suicide			
subjects affected / exposed	1 / 838 (0.12%)	0 / 224 (0.00%)	0 / 478 (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
Depression			
subjects affected / exposed	0 / 838 (0.00%)	0 / 224 (0.00%)	1 / 478 (0.21%)
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, Auditory			

subjects affected / exposed	0 / 838 (0.00%)	1 / 224 (0.45%)	0 / 478 (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
Mental Disorder			
subjects affected / exposed	0 / 838 (0.00%)	0 / 224 (0.00%)	0 / 478 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mixed Anxiety and Depressive Disorder			
subjects affected / exposed	0 / 838 (0.00%)	0 / 224 (0.00%)	1 / 478 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic Disorder			
subjects affected / exposed	0 / 838 (0.00%)	0 / 224 (0.00%)	1 / 478 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic Disorder			
subjects affected / exposed	3 / 838 (0.36%)	2 / 224 (0.89%)	1 / 478 (0.21%)
occurrences causally related to treatment / all	1 / 3	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic Symptom			
subjects affected / exposed	0 / 838 (0.00%)	0 / 224 (0.00%)	1 / 478 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	6 / 838 (0.72%)	1 / 224 (0.45%)	8 / 478 (1.67%)
occurrences causally related to treatment / all	2 / 6	0 / 1	4 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal Ideation			
subjects affected / exposed	3 / 838 (0.36%)	2 / 224 (0.89%)	1 / 478 (0.21%)
occurrences causally related to treatment / all	2 / 4	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide Attempt			

subjects affected / exposed	2 / 838 (0.24%)	0 / 224 (0.00%)	2 / 478 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur Fracture			
subjects affected / exposed	0 / 838 (0.00%)	1 / 224 (0.45%)	0 / 478 (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
Limb Injury			
subjects affected / exposed	0 / 838 (0.00%)	1 / 224 (0.45%)	0 / 478 (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
Radius Fracture			
subjects affected / exposed	0 / 838 (0.00%)	0 / 224 (0.00%)	1 / 478 (0.21%)
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			
Atrial Fibrillation			
subjects affected / exposed	1 / 838 (0.12%)	0 / 224 (0.00%)	0 / 478 (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
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 838 (0.00%)	0 / 224 (0.00%)	1 / 478 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal Obstruction			
subjects affected / exposed	0 / 838 (0.00%)	0 / 224 (0.00%)	1 / 478 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	0 / 838 (0.00%)	1 / 224 (0.45%)	0 / 478 (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
Renal and urinary disorders			
Pelvi-Ureteric Obstruction			
subjects affected / exposed	0 / 838 (0.00%)	0 / 224 (0.00%)	1 / 478 (0.21%)
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			
Rotator Cuff Syndrome			
subjects affected / exposed	1 / 838 (0.12%)	0 / 224 (0.00%)	0 / 478 (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
Infections and infestations			
Furuncle			
subjects affected / exposed	1 / 838 (0.12%)	0 / 224 (0.00%)	0 / 478 (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
Pneumonia			
subjects affected / exposed	1 / 838 (0.12%)	0 / 224 (0.00%)	0 / 478 (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

Serious adverse events	Follow-up (FU) Phase PP3M	Follow-up (FU) Phase PP6M	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 42 (2.38%)	6 / 109 (5.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain Neoplasm			
subjects affected / exposed	0 / 42 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Lymphocytic Leukaemia			

subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal Sinus Cancer			
subjects affected / exposed	0 / 42 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm Malignant			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Artery Occlusion			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Mammoplasty			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			

subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Death			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Priapism			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute Psychosis			

subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adjustment Disorder with Mixed Anxiety and Depressed Mood			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adjustment Disorder with Mixed Disturbance of Emotion and Conduct			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol Withdrawal Syndrome			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Behavioural Addiction			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed Suicide			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, Auditory			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental Disorder			

subjects affected / exposed	0 / 42 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mixed Anxiety and Depressive Disorder			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic Disorder			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic Disorder			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic Symptom			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	0 / 42 (0.00%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal Ideation			
subjects affected / exposed	1 / 42 (2.38%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide Attempt			
subjects affected / exposed	0 / 42 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Femur Fracture			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb Injury			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius Fracture			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal Obstruction			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Pelvi-Ureteric Obstruction			

subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rotator Cuff Syndrome			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Furuncle			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Open Label (OL) PP1M/PP3M (4 Months)	Double-blind (DB) Phase PP3M	Double-blind (DB) Phase PP6M
Total subjects affected by non-serious adverse events			
subjects affected / exposed	127 / 838 (15.16%)	52 / 224 (23.21%)	125 / 478 (26.15%)
Investigations			
Weight Increased			
subjects affected / exposed	8 / 838 (0.95%)	17 / 224 (7.59%)	40 / 478 (8.37%)
occurrences (all)	8	17	40
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 838 (1.91%)	12 / 224 (5.36%)	32 / 478 (6.69%)
occurrences (all)	25	16	61
General disorders and administration site conditions			
Injection Site Pain			

subjects affected / exposed	72 / 838 (8.59%)	9 / 224 (4.02%)	37 / 478 (7.74%)
occurrences (all)	123	10	57
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	22 / 838 (2.63%)	13 / 224 (5.80%)	22 / 478 (4.60%)
occurrences (all)	22	16	27
Upper Respiratory Tract Infection			
subjects affected / exposed	19 / 838 (2.27%)	9 / 224 (4.02%)	24 / 478 (5.02%)
occurrences (all)	21	9	48

Non-serious adverse events	Follow-up (FU) Phase PP3M	Follow-up (FU) Phase PP6M	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 42 (2.38%)	5 / 109 (4.59%)	
Investigations			
Weight Increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Injection Site Pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 109 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 42 (2.38%)	4 / 109 (3.67%)	
occurrences (all)	1	4	
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 42 (0.00%)	1 / 109 (0.92%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 March 2018	a) Clarified text (1) on the version of Columbia Suicide Severity Rating Scale (C-SSRS) to be used at the screening and baseline visits, and all other visits; (2) vital signs to be collected every 3 months (Q3) during Double-blind (DB) Phase; (3) on the frequency of pre study Risperdal injections, and that subjects taking branded LAI of risperidone or paliperidone palmitate (PP) were permitted to enter the Transition Phase of the study. b) Added text (1) to maximize patient safety, exclude clinically unstable patients, and align with the R092670PSY3011 protocol; (2) to modify exclusion criterion #10 to minimize risk of fetal exposure to study drug; (3) to include risperidone 3 mg/day as a valid alternative at an equivalent dose in countries for which the paliperidone ER/prolonged-release (PR) formulations was not available; (3) to provide clearer guidance on timing of the end-of phase (EOP) visit; (4) to update Attachment 1 "Guidelines for the Intramuscular Injection of Paliperidone Palmitate or Placebo During the DB Phase" with clear instructions regarding the administration of injection; (5) to add exclusion criterion #26 excluding subjects with severe renal impairment per FDA request for clarification; (6) to add a formula to clarify the calculation of percent change of PANSS total score. c) Modified text (1) to remove renal insufficiency as part of exclusion criterion #7; (2) to limit participation in the Transition Phase to subjects taking INVEGA SUSTENNA or XEPLION PP1M formulations (3) to modify text to prevent the risk of unblinding study treatment while collecting prolactin samples for clinical laboratory testing; (4) to remove controlling stratification by the maintenance dose level in the primary efficacy analysis. Two hundred sixteen subjects were enrolled in the study under the original protocol and 464 subjects were enrolled under the first protocol amendment.
28 September 2018	a) Revised the number of pre-randomization injections of PP1M from a total of 6 (i.e., 5-month duration) to a total of 5 (i.e., 4-month duration) required before subjects were randomized to either PP3M or PP6M (paliperidone palmitate [PP] treatment group in the Double-blind Phase. This change was applied to subjects in the study's Open-label phases being treated with PP1M after the PP3M pre-randomization target was met, since these subjects were randomized directly from PP1M treatment. b) Updated and clarified supporting text, figures, and tables for consistency and to correct conflicting portions of the protocol that inadvertently increased the minimum duration of PP1M treatment from 4 months to 5 months. c) Removed text related to optional salivary biomarkers research. Fourteen subjects were enrolled under the second global protocol amendment
11 February 2019	a) To align with the primary endpoint, the duration of the Double-blind Phase was limited to 12 months by eliminating the double-blind extension period. b) The estimated number of subjects entering the Transition/Maintenance Phases was increased from a target sample size of 765 to 840 to match dropout/enrollment rates and to meet the randomization target of 549 subjects in the Double-blind Phase. c) Modified Inclusion Criterion 11 to clarify the method of contraception in criterion 10 was applicable to female partners of male study subjects. d) Removed collection of blood biomarkers from the protocol. The third global amendment was implemented after all subjects had been enrolled.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported