Clinical trial results:
A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Pimavanserin as Adjunctive Treatment for the Negative Symptoms of Schizophrenia

Summary

EudraCT number	2016-003436-20
Trial protocol	HU BG ES CZ PL
Global end of trial date	28 October 2019

Results information

Result version number	v2 (current)
This version publication date	30 January 2021
First version publication date	18 November 2020
Version creation reason	• Correction of full data set Corrections of full data set required

Trial information

Trial identification

Sponsor protocol code	ACP-103-038

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02970305
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Acadia Pharmaceuticals Inc.
Sponsor organisation address	12830 El Camino Real, Suite 400, San Diego, United States, 92130
Public contact	Sr. Dir. Medical Information and Medical Communications, Acadia Pharmaceuticals Inc., 1 8582612897, medicalinformation@acadia-pharm.com
Scientific contact	Sr. Dir. Medical Information and Medical Communications, Acadia Pharmaceuticals Inc., 1 8582612897, medicalinformation@acadia-pharm.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	16 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 October 2019
Global end of trial reached?	Yes
Global end of trial date	28 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of pimavanserin compared with placebo in the adjunctive treatment of the negative symptoms of schizophrenia

Protection of trial subjects:

Not applicable

Background therapy:

Patients were to continue their main background antipsychotic medication

Evidence for comparator: -

Actual start date of recruitment	04 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Bulgaria: 91
Country: Number of subjects enrolled	Czech Republic: 23
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Serbia: 68
Country: Number of subjects enrolled	Russian Federation: 100
Country: Number of subjects enrolled	Ukraine: 40
Country: Number of subjects enrolled	United States: 49
Worldwide total number of subjects	403
EEA total number of subjects	146

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	403
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study enrolled patients with predominant negative symptoms of schizophrenia, using antipsychotic treatment from a protocol-defined list of allowed treatments. The main antipsychotic treatment was to be continued during the study; adjustments to the dose of the main antipsychotic were not permitted after completion of the screening period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pimavanserin

Arm description:

Treatment was to be started at a daily dose of pimavanserin 20 mg; this dose was to be continued for the first 2 weeks of treatment. Subsequently, during the flexible-dosing period of double-blind treatment period (Weeks 2-8), the dose could be continued unchanged, increased to up to 34 mg daily, or decreased to up to 10 mg daily at the investigator’s discretion, based on clinical benefit and safety/tolerability. No dose adjustments were allowed during the fixed-dosing period of the double-blind treatment period (Weeks 8-26).

Patients were to continue their background antipsychotic treatment

Arm type	Experimental
Investigational medicinal product name	Pimavanserin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment was to be started at a daily dose of pimavanserin 20 mg; this dose was to be continued for the first 2 weeks of treatment . Subsequently, during the flexible-dosing period of double-blind treatment period (Weeks 2-8), the dose could be continued unchanged, increased to up to 34 mg daily, or decreased to up to 10 mg daily at the investigator’s discretion, based on clinical benefit and safety/tolerability. No dose adjustments were allowed during the fixed-dosing period of the double-blind treatment period (Weeks 8-26).

Arm title	Placebo

Arm description:

Pimavanserin-matching Placebo.
Patients were to continue their background main antipsychotic treatment

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pimavanserin matching placebo once daily

Number of subjects in period 1	Pimavanserin	Placebo
Started	201	202
Completed	172	174
Not completed	29	28
Consent withdrawn by subject	12	11
Adverse event, non-fatal	10	6
Noncompliance with study drug	2	4
Lost to follow-up	1	2
Not further specified	1	2
Lack of efficacy	1	1
Protocol deviation	2	2

Baseline characteristics

Reporting groups

Reporting group title	Pimavanserin

Reporting group description:

Treatment was to be started at a daily dose of pimavanserin 20 mg; this dose was to be continued for the first 2 weeks of treatment. Subsequently, during the flexible-dosing period of double-blind treatment period (Weeks 2-8), the dose could be continued unchanged, increased to up to 34 mg daily, or decreased to up to 10 mg daily at the investigator's discretion, based on clinical benefit and safety/tolerability. No dose adjustments were allowed during the fixed-dosing period of the double-blind treatment period (Weeks 8-26).

Patients were to continue their background antipsychotic treatment

Reporting group title	Placebo

Reporting group description:

Pimavanserin-matching Placebo.
Patients were to continue their background main antipsychotic treatment

Reporting group values	Pimavanserin	Placebo	Total
Number of subjects	201	202	403
Age categorical Units: Subjects			
Adults (18-64 years)	201	202	403
Age continuous Units: years			
arithmetic mean	37.7	36.7	
standard deviation	± 9.37	± 9.24	-
Gender categorical Units: Subjects			
Female	70	65	135
Male	131	137	268
Schizophrenia diagnosis confirmed by SCID-5-CT			
SCID-5-CT: Structured Clinical Interview for DSM-5, Clinical Trials Version			
Units: Subjects			
Schizophrenia diagnosis confirmed by SCID-5-CT	201	202	403

End points

End points reporting groups

Reporting group title	Pimavanserin

Reporting group description:

Treatment was to be started at a daily dose of pimavanserin 20 mg; this dose was to be continued for the first 2 weeks of treatment. Subsequently, during the flexible-dosing period of double-blind treatment period (Weeks 2-8), the dose could be continued unchanged, increased to up to 34 mg daily, or decreased to up to 10 mg daily at the investigator's discretion, based on clinical benefit and safety/tolerability. No dose adjustments were allowed during the fixed-dosing period of the double-blind treatment period (Weeks 8-26).

Patients were to continue their background antipsychotic treatment

Reporting group title	Placebo

Reporting group description:

Pimavanserin-matching Placebo.
Patients were to continue their background main antipsychotic treatment

Primary: Change From Baseline to Week 26 in the Negative Symptom Assessment-16 (NSA-16) Total Score

End point title	Change From Baseline to Week 26 in the Negative Symptom Assessment-16 (NSA-16) Total Score

End point description:

The NSA-16 is a semi-structured interview and a validated scale containing 16 items for evaluating negative symptoms of schizophrenia, i.e. the reduction or absence of emotional expression and volitional behaviors normally present in a healthy person. Items are scored based on behaviors during the interview (items 1-4, 6, 7, 9, 11, 15, 16) or previous 7 days (items 5, 8, 10, 12-14) on a 6-point scale from 1 to 6. The NSA-16 total score is the sum of item scores. It can range from 16 to a maximum of 96, with higher scores denoting more severe negative symptoms in schizophrenia.

End point type	Primary

End point timeframe:

From baseline to Week 26

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199[1]	201[2]		
Units: Score on a scale				
arithmetic mean (standard error)				
Baseline	61.8 (± 0.60)	61.0 (± 0.61)		
Change from baseline to Week 26	-10.5 (± 0.69)	-8.8 (± 0.69)		

Notes:

[1] - 199 at baseline; 174 at Week 26

[2] - 201 at baseline; 173 at Week 26

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Placebo v Pimavanserin

Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0434
Method	Mixed-effects model for repeated measure
Parameter estimate	Difference in MMRM LSMs
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.95

Secondary: Change From Baseline to Week 26 in the Personal and Social Performance Scale (PSP) Score

End point title	Change From Baseline to Week 26 in the Personal and Social Performance Scale (PSP) Score

End point description:

The PSP is a validated 100-point (1 to100) single-item rating scale to assess the psychosocial functioning of subjects with schizophrenia. Ratings are based on 4 main areas i.e. (a) socially useful activities, including work and study; (2) personal and social relationships, (3) self-care; and (4) disturbing and aggressive behaviors. The time period assessed is "past month". Higher scores denote better psychosocial functioning

End point type	Secondary

End point timeframe:

From baseline to Week 26

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199[3]	201[4]		
Units: Score on a scale				
arithmetic mean (standard error)				
Baseline	47.2 (± 0.83)	46.7 (± 0.76)		
Change from baseline to Week 26	8.1 (± 0.70)	8.4 (± 0.75)		

Notes:

[3] - 199 at baseline; 174 at Week 26

[4] - 201 at baseline; 173 at Week 26

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of NSA-16 Responders at Week 26

End point title	Proportion of NSA-16 Responders at Week 26

End point description:

The NSA-16 is a semi-structured interview and a validated scale containing 16 items for evaluating

negative symptoms of schizophrenia, i.e. the reduction or absence of emotional expression and volitional behaviors normally present in a healthy person. Items are scored based on behaviors during the interview (items 1-4, 6, 7, 9, 11, 15, 16) or previous 7 days (items 5, 8, 10, 12-14) on a 6-point scale from 1 to 6. The NSA-16 total score is the sum of item scores. It can range from 16 to a maximum of 96, with higher scores denoting more severe negative symptoms in schizophrenia.
NSA-16 responders were defined as patients with at least 20, 30, 50, or 75% percentage improvement in NSA-16 total score from baseline.

End point type	Secondary

End point timeframe:

From baseline to Week 26

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	173		
Units: Patients				
At least 20% improvement	93	84		
At least 30% improvement	56	51		
At least 50% improvement	21	16		
At least 75% improvement	4	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 26 in NSA-16 Global Negative Symptoms Rating

End point title	Change From Baseline to Week 26 in NSA-16 Global Negative Symptoms Rating

End point description:

The global negative symptoms rating of the NSA-16 assesses overall severity on a 7-point scale from 1 to 7, with higher scores denoting more severe negative symptoms in schizophrenia.

End point type	Secondary

End point timeframe:

From baseline to Week 26

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199[5]	201[6]		
Units: Score on a scale				
arithmetic mean (standard error)				
Baseline	4.7 (± 0.05)	4.8 (± 0.05)		
Change from baseline to Week 26	-0.7 (± 0.06)	-0.7 (± 0.06)		

Notes:

[5] - 199 at baseline; 174 at Week 26

[6] - 201 at baseline; 173 at Week 26

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline (CFB) to Week 26 in NSA-16 Domain Scores

End point title	Change From Baseline (CFB) to Week 26 in NSA-16 Domain Scores

End point description:

The NSA-16 is a semi-structured interview and a validated scale containing 16 items for evaluating negative symptoms of schizophrenia, i.e. the reduction or absence of emotional expression and volitional behaviors normally present in a healthy person. Items are scored based on behaviors during the interview (items 1-4, 6, 7, 9, 11, 15, 16) or previous 7 days (items 5, 8, 10, 12-14) on a 6-point scale from 1 to 6. The NSA-16 domain scores are the sum of item scores in each domain i.e. communication (min score 4, max score 24), emotion/affect (min 3, max 18), social Involvement (min 3, max 18), motivation (min 4, max 24), and retardation (min 2, max 12); with higher scores denoting more severe negative symptoms in schizophrenia.

End point type	Secondary

End point timeframe:

From baseline to Week 26

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199[7]	201[8]		
Units: Score on a scale				
arithmetic mean (standard error)				
Communication, baseline	12.3 (± 0.22)	12.3 (± 0.21)		
Communication, CFB to Week 26	-2.4 (± 0.21)	-2.0 (± 0.19)		
Emotion/affect, baseline	12.7 (± 0.14)	12.5 (± 0.15)		
Emotion/affect, CFB to Week 26	-1.9 (± 0.17)	-1.6 (± 0.15)		
Social involvement, baseline	13.1 (± 0.16)	12.6 (± 0.18)		
Social involvement, CFB to Week 26	-2.0 (± 0.17)	-1.4 (± 0.19)		
Retardation, baseline	7.0 (± 0.12)	7.0 (± 0.12)		
Retardation, CFB to Week 26	-1.7 (± 0.13)	-1.5 (± 0.13)		
Motivation, baseline	16.7 (± 0.18)	16.6 (± 0.18)		
Motivation, CGB to Week 26	-2.6 (± 0.20)	-2.2 (± 0.23)		

Notes:

[7] - BL: 199 (E/A, S, M: 198);
W26: 174 (E/A: 171, SI, M: 173)
[8] - BL: 201 (E/A: 200, SI: 199);
W26: 173 (E/A, SI: 172)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 26 in CGI-SCH-S of Negative Symptoms Score

End point title	Change From Baseline to Week 26 in CGI-SCH-S of Negative Symptoms Score

End point description:

The Clinical Global Impression of Schizophrenia Scale-Severity (CGI-SCH-S) of Negative Symptom scoreis a clinician-rated, 7-point scale to evaluate positive, negative, depressive, cognitive symptoms and overall severity in schizophrenia. For the purpose of this study, only the negative symptoms were evaluated. The score could range from 1 (normal, not ill) to 7 (among the most severely ill).

End point type	Secondary

End point timeframe:

From baseline to Week 26

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199[9]	201[10]		
Units: Score on a scale				
arithmetic mean (standard error)				
Baseline	4.6 (± 0.04)	4.7 (± 0.04)		
Change from baseline to W26	-0.6 (± 0.06)	-0.6 (± 0.06)		

Notes:

[9] - 199 at baseline; 174 at Week 26

[10] - 201 at baseline; 173 at Week 26

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression of Schizophrenia Scale-Improvement (CGI-SCH-I) of Negative Symptoms Score at Week 26

End point title	Clinical Global Impression of Schizophrenia Scale-Improvement (CGI-SCH-I) of Negative Symptoms Score at Week 26

End point description:

The CGI-SCH-I is a clinician-rated, 7-point scale to evaluate change from baseline in positive, negative, depressive, cognitive symptoms and overall severity in schizophrenia. For the purpose of this study, only the changes in negative symptoms from baseline were evaluated. The score could range from 1 (very much improved) to 7 (very much worse).

End point type	Secondary

End point timeframe:

From baseline to Week 26

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	173		
Units: Score on a scale				
arithmetic mean (standard error)	3.1 (± 0.07)	3.1 (± 0.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of CGI-SCH-I Responders (CGI-SCH-I Score of 1 or 2) at Week 26; Observed Cases

End point title	Proportion of CGI-SCH-I Responders (CGI-SCH-I Score of 1 or 2) at Week 26; Observed Cases

End point description:

The CGI-SCH-I is a clinician-rated, 7-point scale that is designed to evaluate change from baseline in positive, negative, depressive, cognitive symptoms and overall severity in schizophrenia. For the purpose of this study, only the changes in negative symptoms from baseline were evaluated. The 7-point scores range from 1 (very much improved) to 7 (very much worse); responders were defined as those with CGI-SCH-I of 1 or 2.
The analysis includes observed cases; missing cases were not imputed.

End point type	Secondary

End point timeframe:

From baseline to Week 26

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	173		
Units: Patients	47	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 26 in the Positive and Negative Syndrome Scale (PANSS) Total Score

End point title	Change From Baseline to Week 26 in the Positive and Negative Syndrome Scale (PANSS) Total Score

End point description:

The PANSS is a 30-item scale to evaluate the presence, absence, and severity of schizophrenia symptoms. Items are scored over the past week (7 days) on a 7-point scale from 1 (absent) to 7 (extreme). The PANSS total score is the sum of scores and ranges from a minimum of 30 to a maximum of 210. Higher scores denote more severe symptoms.

End point type	Secondary

End point timeframe:

From baseline to Week 26

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199[11]	201[12]		
Units: Score on a scale				
arithmetic mean (standard error)				
Baseline	77.2 (± 0.70)	79.4 (± 0.62)		
Change from baseline to Week 26	-8.7 (± 0.75)	-8.6 (± 0.76)		

Notes:

[11] - 199 at baseline; 174 at Week 26

[12] - 201 at baseline; 173 at Week 26

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline (CFB) to Week 26 in PANSS Subscale Scores

End point title	Change From Baseline (CFB) to Week 26 in PANSS Subscale Scores

End point description:

The PANSS is a 30-item scale to evaluate the presence, absence, and severity of schizophrenia symptoms. Items are scored over the past week (7 days) on a 7-point scale from 1 (absent) to 7 (extreme). The PANSS has 3 subscales that are the sums of the respective item scores, including the positive scale (min 7, max 49), negative scale (min 7, max 49), and general psychopathology scale (min 16, max 112). Higher scores denote more severe symptoms.

End point type	Secondary

End point timeframe:

From baseline to Week 26

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199[13]	201[14]		
Units: Score on a scale				
arithmetic mean (standard error)				
Positive subscale, baseline	13.1 (± 0.24)	13.7 (± 0.22)		
Positive subscale, CFB to Week 26	-0.6 (± 0.19)	-0.8 (± 0.21)		
Negative subscale, baseline	27.5 (± 0.26)	27.5 (± 0.25)		
Negative subscale, CFB to Week 26	-4.0 (± 0.29)	-3.8 (± 0.31)		
Gen psychopathology subscale, baseline	36.6 (± 0.44)	38.2 (± 0.40)		
Gen psychopathology subscale, CFB to Week 26	-4.1 (± 0.43)	-4.0 (± 0.43)		

Notes:

[13] - 199 at baseline, 174 at Week 26

[14] - 201 at baseline; 173 at Week 26

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 26 in Brief Assessment of Cognition in Schizophrenia (BACS) Score

End point title	Change From Baseline to Week 26 in Brief Assessment of Cognition in Schizophrenia (BACS) Score

End point description:

The BACS is a performance-based assessment of treatment-related changes in cognition, assessing 6 domains of verbal memory and learning; working memory; motor function; verbal fluency; attention and speed of processing; and executive function. The 6 domains with their raw scores are: verbal memory 0-75; digit sequencing 0-28; token motor 0-100; verbal fluency 0-225; symbol coding 0-110; Tower of London 0-22. For each domain, higher scores reflect better cognition. Raw scores are converted to age and sex-corrected normalized scores. The BACS composite score is calculated as the mean of the normalized scores from the 6 subscale scores, standardized so that the mean of the BACS composite score in the healthy normative sample is 50 and the standard deviation is 10.

End point type	Secondary

End point timeframe:

From baseline to Week 26

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197[15]	199[16]		
Units: Score on a scale				
arithmetic mean (standard error)				
Baseline	22.94 (± 1.271)	20.99 (± 1.198)		
Change from baseline to Week 26	3.33 (± 0.719)	4.16 (± 0.696)		

Notes:

[15] - 197 at baseline; 173 at Week 26

[16] - 199 at baseline; 170 at Week 26

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 26 in 10-item Drug Attitude Inventory (DAI-10) Score

End point title	Change From Baseline to Week 26 in 10-item Drug Attitude Inventory (DAI-10) Score

End point description:

The DAI-10 contains 6 items (1, 3, 4, 7, 9, and 10) that a subject who is fully adherent to the prescribed medication would answer as "True" and 4 items (2, 5, 6, and 8) that a subject who is fully adherent to the prescribed medication would answer as "False." A correct answer is scored +1 and an incorrect answer is scored -1. The total score is the sum of pluses and minuses, which can range from -10 to 10 in increments of 2. A positive total score indicates a positive subjective response (adherent) and a negative total score indicates a negative subjective response (nonadherent). Higher scores denote better adherence.

End point type	Secondary

End point timeframe:

From baseline to Week 26

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199[17]	201[18]		
Units: Score on a scale				
arithmetic mean (standard error)				
Baseline	5.7 (± 0.22)	5.7 (± 0.23)		
Change from baseline to Week 26	0.2 (± 0.23)	0.2 (± 0.19)		

Notes:

[17] - 199 at baseline; 174 at Week 26

[18] - 201 at baseline; 173 at Week 26

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 26 in Karolinska Sleepiness Scale (KSS) Score

End point title	Change From Baseline to Week 26 in Karolinska Sleepiness Scale (KSS) Score

End point description:

The KSS is a self-reported subjective measure of a subject's level of drowsiness. Respondents must choose statements that most accurately describe their level of sleepiness over the past 7 days. Scoring was based on a 9-point verbally anchored scale ranging from 1 (extremely alert) to 9 (very sleepy, great effort to keep awake, fighting sleep). Higher scores denoted more drowsiness.

End point type	Secondary

End point timeframe:

Change from baseline to Week 26

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199[19]	201[20]		
Units: Score on a scale				
arithmetic mean (standard error)				
Baseline	4.6 (± 0.11)	4.8 (± 0.10)		
Change from baseline to Week 26	-0.3 (± 0.12)	-0.6 (± 0.13)		

Notes:

[19] - 199 at baseline; 174 at Week 26

[20] - 201 at baseline; 173 at Week 26

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of the first dose of study drug until 30 days after the last dose of study drug planned to be administered at Week 26

Adverse event reporting additional description:

The analysis population were all patients randomised and treated (i.e. receiving at least one dose of study drug).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Pimavanserin

Reporting group description:

Treatment was to be started at a daily dose of pimavanserin 20 mg; this dose was to be continued for the first 2 weeks of treatment . Subsequently, during the flexible-dosing period of double-blind treatment period (Weeks 2-8), the dose could be continued unchanged, increased to up to 34 mg daily, or decreased to up to 10 mg daily at the investigator's discretion, based on clinical benefit and safety/tolerability. No dose adjustments were allowed during the fixed-dosing period of the double-blind treatment period (Weeks 8-26).
Patients were to continue their background antipsychotic treatment

Reporting group title	Placebo

Reporting group description:

Pimavanserin-matching Placebo.
Patients were to continue their background main antipsychotic treatment

Serious adverse events	Pimavanserin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 201 (1.99%)	1 / 202 (0.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	4 / 201 (1.99%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pimavanserin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 201 (9.95%)	19 / 202 (9.41%)	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 201 (6.47%)	10 / 202 (4.95%)	
occurrences (all)	17	10	
Somnolence			
subjects affected / exposed	11 / 201 (5.47%)	10 / 202 (4.95%)	
occurrences (all)	12	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 November 2016	The following key changes were implemented: - Safety follow-up period extended to 4 weeks - Number of sites increased to 70 - Inclusion criteria amended to: state that patients must have been medically stable for at least 12 weeks before Screening; remove requirement for abstinence during and at least 1 month after completion of the study - Exclusion criteria amended to: include history of uncontrolled diabetes mellitus Type 1 or 2 requiring insulin; exclude patients with history of suicide attempts or currently actively suicidal or at imminent risk of self-harm - Test product updated to include 17 mg tablets and matching placebo - Dose updated to include pimavanserin (or matching placebo) 34 mg - Informed consent updated to include written agreement from the patient's caregiver - Blood sample collection, screening, PK statistical methods updated to confirm presence or absence of the identified main antipsychotic - Added population PK/PD model for exposure response relationship between pimavanserin plasma concentrations and efficacy and safety parameters - Prohibition/restriction of drugs prolonging QT interval; prohibition of strong cytochrome CYP3A4 Inhibitors; introduced rules to discontinue CYP3A4 Inhibitors/inducers - Introduced possibility to discontinue patients with <80% or >120% compliance from the study - PANSS updated to include the caregiver-reported IQ-PANSS - Added reporting of overdose within 24 hours of discovery
31 March 2017	- Inclusion criteria amended to: specify age as ≥18 and ≤55 years; delete requirement for ≤10 years treatment with an antipsychotic - Exclusion criteria amended to: allow patients with presence of marijuana based on laboratory testing (but patient had to abstain from marijuana use during the study); added exclusion criterion of social hospitalization in the last 8 weeks - Updated data required to be selected at PK sampling - PK assessment procedures and endpoints updated Screening period requirements were updated to include subjects up to age ≤55 and preference for enrollment of an equal number of subjects who are ≤35 and who are >35 years old. - Allowed a single documented social hospitalization for a maximum duration of 2 weeks over the course of the study. - AE collection period updated - Several updates to statistical methods and testing strategy - Added anticholinergic restrictions; modified rules for anxiolytics to allow patients on a stable dose at study entry

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported

Notes: