Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Adjunctive Pimavanserin for the Treatment of Schizophrenia

Summary

EudraCT number	2016-003434-24
Trial protocol	HU BG CZ LT PL
Global end of trial date	25 June 2019

Results information

Result version number	v1 (current)
This version publication date	18 November 2020
First version publication date	18 November 2020

Trial information

Trial identification

Sponsor protocol code	ACP-103-034

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02970292
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Acadia Pharmaceuticals Inc.
Sponsor organisation address	3611 Valley Centre Drive, Ste. 300, 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	28 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 May 2019
Global end of trial reached?	Yes
Global end of trial date	25 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the efficacy of adjunctive pimavanserin compared with adjunctive placebo in the treatment of schizophrenia

Protection of trial subjects:

Not applicable

Background therapy:

Patients were to continue intake of their antipsychotic treatment

Evidence for comparator: -

Actual start date of recruitment	26 October 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	Canada: 2
Country: Number of subjects enrolled	Russian Federation: 90
Country: Number of subjects enrolled	Serbia: 77
Country: Number of subjects enrolled	Ukraine: 40
Country: Number of subjects enrolled	United States: 71
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Bulgaria: 93
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Lithuania: 9
Worldwide total number of subjects	396
EEA total number of subjects	116

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)	396
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was performed between 26 Oct 2016 (first patient consented) and 25 Jun 2019 (last patient last visit).

Pre-assignment

Screening details:

Eligible patients had to be taking an adequate dose of an antipsychotic, in the dose range recommended by the local product information, for >=8 weeks before screening. For patients taking 2 antipsychotics, the main antipsychotic was determined and continued, while the second antipsychotic was discontinued (if clinically appropriate).

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:

Patients started treatment with pimavanserin 20 mg once daily (QD). At the Week 1, Week 2 and Week 3 visit, the dose could be increased to 34 mg QD or decreased to 10 mg QD at the investigator’s discretion. Thereafter, the daily dose was to remain the same for the remainder of the study.
Patients were to continue their background, main 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:

Patients started treatment with pimavanserin 20 mg once daily (QD). At the Week 1, Week 2 and Week 3 visit, the dose could be increased to 34 mg QD or decreased to 10 mg QD at the investigator’s discretion (to improve symptom reliev or tolerability, respectively). Thereafter, the daily dose was to remain the same for the remainder of the study.
Each daily dose consisted of 2 individual tablets that were to be taken together at approximately the same time each day as the patient's main antipsychotic.

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.
Each daily dose consisted of 2 individual tablets that were to be taken together at approximately the same time each day as the patient's main antipsychotic.

Number of subjects in period 1	Pimavanserin	Placebo
Started	198	198
Completed	174	190
Not completed	24	8
Consent withdrawn by subject	11	5
Physician decision	1	1
Adverse event, non-fatal	5	-
Not specified	1	-
Noncompliance with study drug	2	2
Lost to follow-up	1	-
Lack of efficacy	1	-
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Pimavanserin
Reporting group description:	
Patients started treatment with pimavanserin 20 mg once daily (QD). At the Week 1, Week 2 and Week 3 visit, the dose could be increased to 34 mg QD or decreased to 10 mg QD at the investigator's discretion. Thereafter, the daily dose was to remain the same for the remainder of the study. Patients were to continue their background, main 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	198	198	396
Age categorical Units: Subjects			
Adults (18-64 years)	198	198	396
Age continuous Units: years			
arithmetic mean	36.8	37.4	
standard deviation	± 9.42	± 9.45	-
Gender categorical Units: Subjects			
Female	72	78	150
Male	126	120	246

End points

End points reporting groups

Reporting group title	Pimavanserin
Reporting group description:	
Patients started treatment with pimavanserin 20 mg once daily (QD). At the Week 1, Week 2 and Week 3 visit, the dose could be increased to 34 mg QD or decreased to 10 mg QD at the investigator's discretion. Thereafter, the daily dose was to remain the same for the remainder of the study. Patients were to continue their background, main 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 6 in the Positive and Negative Syndrome Scale (PANSS) Total Score

End point title	Change From Baseline to Week 6 in the Positive and Negative Syndrome Scale (PANSS) Total Score
End point description:	
The PANSS is a 30-item scale used to evaluate the presence, absence, and severity of schizophrenia symptoms. The 30 items are arranged as 7 positive symptom items (P1 to P7), 7 negative symptom items (N1 to N7), and 16 general psychopathology symptom items (G1 to G16). Items are scored over the past week (7 days) on a 7-point scale ranging from 1 (absent) to 7 (extreme). The PANSS total score can range from a minimum of 30 to a maximum of 210, where a higher score signifies greater severity of schizophrenia symptoms.	
End point type	Primary
End point timeframe:	
From baseline to Week 6	

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193[1]	196[2]		
Units: Score points				
arithmetic mean (standard error)				
Baseline	88.3 (± 0.68)	88.1 (± 0.61)		
Change from baseline to Week 6	-15.3 (± 0.93)	-13.4 (± 0.83)		

Notes:

[1] - 193 at baseline; 173 at Week 6

[2] - 196 at baseline; 189 at Week 6

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Pimavanserin v Placebo

Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094
Method	Mixed-effects model for repeated measure
Parameter estimate	Difference in MMRM LSMs
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	0.4
Variability estimate	Standard error of the mean
Dispersion value	1.24

Secondary: Change From Baseline to Week 6 in the Clinical Global Impression-Severity (CGI-S) Score

End point title	Change From Baseline to Week 6 in the Clinical Global Impression-Severity (CGI-S) Score

End point description:

The CGI-S is a 1-item scale, used to rate the severity of the disorder from 0 (not assessed) to 7 (among the most extremely ill patients). A higher CGI-S score denotes greater severity of the disorder.

End point type	Secondary

End point timeframe:

From baseline to Week 6

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193[3]	196[4]		
Units: Score points				
arithmetic mean (standard error)				
Baseline	4.6 (± 0.04)	4.6 (± 0.04)		
Change from baseline to Week 6	-0.8 (± 0.06)	-0.7 (± 0.05)		

Notes:

[3] - 193 at baseline; 173 at Week 6

[4] - 196 at baseline; 189 at Week 6

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline (CFBL) to Week 6 in PANSS Subscale Scores

End point title	Change From Baseline (CFBL) to Week 6 in PANSS Subscale Scores

End point description:

The Subscale Scores were: the PANSS Positive Subscale Score, PANSS Negative Subscale Score and PANSS General Psychopathological Scale Score.

The PANSS is a 30-item scale used to evaluate the presence, absence, and severity of schizophrenia symptoms. The 30 items are arranged as 7 positive symptom items (P1 to P7), 7 negative symptom items (N1 to N7), and 16 General psychopathology symptom items (G1 to G16). Items are scored over the past week (7 days) on a 7-point scale ranging from 1 (absent) to 7 (extreme).
The PANSS positive subscale score can range from 7 to 49; the PANSS negative subscale score can range from 7 to 49; the PANSS general psychopathology scale score can range from 16 to 112.
For each of the subscale scores, a higher score signifies greater severity of schizophrenia symptoms.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193[5]	196[6]		
Units: Score points				
arithmetic mean (standard error)				
PANSS positive scale BL	23.0 (± 0.25)	22.8 (± 0.23)		
PANSS positive scale CFBL to Week 6	-5.4 (± 0.34)	-4.9 (± 0.30)		
PANSS negative scale BL	23.0 (± 0.29)	23.1 (± 0.29)		
PANSS negative scale CFBL to Week 6	-2.8 (± 0.28)	-2.1 (± 0.28)		
PANSS general psychopathology scale BL	42.4 (± 0.45)	42.2 (± 0.42)		
PANSS general psychopathology scale CFBL to Week 6	-7.2 (± 0.49)	-6.4 (± 0.47)		

Notes:

[5] - 193 at baseline; 173 at Week 6

[6] - 196 at baseline; 189 at Week 6

Statistical analyses

No statistical analyses for this end point

Secondary: PANSS Responders

End point title	PANSS Responders

End point description:

Porportion of patients showing a PANSS response of >=20% or >=30% reduction in PANSS total score. PANSS total score reduction signifies improvement.

End point type	Secondary

End point timeframe:

From baseline to Week 6

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	196		
Units: Patients				
PANSS total score reduction >=20%	109	99		
PANSS total score reduction >=30%	71	67		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression-Improvement (CGI-I) Response

End point title	Clinical Global Impression-Improvement (CGI-I) Response

End point description:

The CGI-I is a 1-item scale, used to rate the improvement from 1 (very much improved) to 7 (very much worse). Higher scores denote less improvement.
A CGI-I score of 1 or 2 was counted as response. The Analysis was performed twice; once including missing values as non-responders (MN) and once including only observed cases (OC).

End point type	Secondary

End point timeframe:

From baseline to Week 6

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193[7]	196[8]		
Units: Patients				
CGI-I response (MN)	68	65		
CGI-I response (OC)	68	65		

Notes:

[7] - 193 for CGI-I Response (MN); 173 for CGI-I Response (OC)

[8] - 196 for CGI-I Response (MN); 189 for CGI-I Response (OC)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression-Improvement (CGI-I) Score at Week 6

End point title	Clinical Global Impression-Improvement (CGI-I) Score at Week 6

End point description:

The CGI-I is a 1-item scale, used to rate the improvement from 1 (very much improved) to 7 (very much worse). Higher scores denote less improvement.

End point type	Secondary

End point timeframe:

From baseline to Week 6

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	189		
Units: Score points				
arithmetic mean (standard error)				
CGI-I Score at Week 6	2.8 (± 0.07)	3.0 (± 0.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 6 in Personal and Social Performance (PSP) Scale Score

End point title	Change From Baseline to Week 6 in Personal and Social Performance (PSP) Scale Score

End point description:

The PSP is a validated 100-point (1 to100) single-item rating scale to assess the psychosocial functioning of patients with schizophrenia. The maximum score is 100. Higher scores denote better psychosocial functioning.

End point type	Secondary

End point timeframe:

From baseline to Week 6

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193[9]	196[10]		
Units: Score points				
arithmetic mean (standard error)				
Baseline	51.8 (± 0.79)	51.6 (± 0.78)		
Change from baseline to Week 6	6.8 (± 0.71)	5.7 (± 0.64)		

Notes:

[9] - 193 at baseline; 173 at Week 6

[10] - 196 at baseline; 188 at Week 6

Statistical analyses

No statistical analyses for this end point

Secondary: Drug Attitude Inventory (DAI-10)

End point title	Drug Attitude Inventory (DAI-10)

End point description:

The DAI-10 contains 6 items (1, 3, 4, 7, 9, and 10) that a patient who is fully adherent to study medication would answer as "True" and 4 items (2, 5, 6, and 8) that a patient who is fully adherent to study medication would answer as "False." A correct answer is scored +1 and an incorrect answer is scored -1; the total score is derived as overall sum. The score can range from -10 to 10. Positive total scores indicate adherence and negative total scores indicate non-adherence. Higher scores denote better adherence.

End point type	Secondary

End point timeframe:

From baseline to Week 6

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193[11]	196[12]		
Units: Score points				
arithmetic mean (standard error)				
Baseline	5.6 (± 0.24)	5.8 (± 0.23)		
Change from baseline to Week 6	0.4 (± 0.20)	0.4 (± 0.20)		

Notes:

[11] - 193 at baseline; 173 at Week 6

[12] - 196 at baseline; 188 at Week 6

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 6 in Karolinska Sleepiness Scale (KSS) Score

End point title	Change From Baseline to Week 6 in Karolinska Sleepiness Scale (KSS) Score

End point description:

The KSS is a self-reported measure of a patient’s level of drowsiness. In this study, drowsiness was to be rated during the last week (7 days). Scoring is based on a 9-point verbally anchored scale ranging from 1 (extremely alert) to 9 (very sleepy, great effort to keep awake, fighting sleep). The maximum score is 9. Higher scores denote more drowsiness.

End point type	Secondary

End point timeframe:

From baseline to Week 6

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193[13]	196[14]		
Units: Score points				
arithmetic mean (standard error)				
Baseline	4.6 (± 0.11)	4.7 (± 0.12)		
Change from baseline to Week 6	-0.5 (± 0.12)	-0.2 (± 0.12)		

Notes:

[13] - 193 at baseline; 173 at Week 6

[14] - 196 at baseline; 189 at Week 6

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to Week 6

Adverse event reporting additional description:

The analysis population were those patients who received at least one dose of the study drug. Patients were classified according to the actual treatment received.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Pimavanserin

Reporting group description:

Patients started treatment with pimavanserin 20 mg once daily (QD). At the Week 1, Week 2 and Week 3 visit, the dose could be increased to 34 mg QD or decreased to 10 mg QD at the investigator's discretion. Thereafter, the daily dose was to remain the same for the remainder of the study.
Patients were to continue their background antipsychotic treatment.

Reporting group title	Placebo

Reporting group description:

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

Serious adverse events	Pimavanserin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 198 (1.01%)	2 / 198 (1.01%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Hallucination, auditory			
subjects affected / exposed	1 / 198 (0.51%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic symptom			
subjects affected / exposed	0 / 198 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			

subjects affected / exposed	1 / 198 (0.51%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Self-injurious ideation			
subjects affected / exposed	0 / 198 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 198 (0.51%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	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	Pimavanserin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 198 (15.66%)	31 / 198 (15.66%)	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 198 (6.57%)	18 / 198 (9.09%)	
occurrences (all)	16	24	
Somnolence			
subjects affected / exposed	13 / 198 (6.57%)	7 / 198 (3.54%)	
occurrences (all)	19	8	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 198 (5.05%)	7 / 198 (3.54%)	
occurrences (all)	10	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 November 2016	The following main changes were introduced: - Increase in the number of participating study sites to 70 - Addition of the US Package Insert for NUPLAZID® (pimavanserin) - Requirement to complete baseline PK sampling before the first dose of study drug; requirement to maintain PK data blinded until the unblinding of the database at the end of the study - Updates to the timing of study drug administration (at approximately the same time as the main antipsychotic medication; guidance in case of missed doses) - Prohibition of strong cytochrome CYP3A4 Inhibitors; introduction of stopping rules for CYP3A4 Inhibitors/inducers - Updates to compliance assessments; introduced possibility to discontinue patients with <80% or >120% compliance from the study - Requirement to measure vital signs before study drug administration - Requirement for a screening blood sample to confirm the presence or absence of the main antipsychotic - Requirement to collect written agreement of the patient's caregiver prior to screening procedures to participate in the study in the caregiver role. - Update of the PANSS to include the caregiver-reported IQ-PANSS
30 March 2017	The following main changes were introduced: - Update of the eligibility criteria for age to be ≥18 and ≤55 years - Addition of PK endpoints - Update of the independent variables in the statistical model to include baseline CGI-S score and baseline-by-visit interaction for CGI-S and PANSS - Update of statistical methods to hierarchical testing procedure to control the type 1 error rate across the primary and key secondary endpoint - Update of the PK statistical method to include the main antipsychotic - Update to the AE collection period for patients rolling over into study ACP-103-035

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported