Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Pimavanserin as Adjunctive Treatment for the Negative Symptoms of Schizophrenia (ADVANCE 2)

Summary

EudraCT number	2019-003343-29
Trial protocol	CZ PL HU BG ES LT IT HR
Global end of trial date	19 February 2024

Results information

Result version number	v1 (current)
This version publication date	26 December 2024
First version publication date	26 December 2024

Trial information

Trial identification

Sponsor protocol code	ACP-103-064

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04531982
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, CA 92130
Public contact	Chelsea Gavilanes, ACADIA Pharmaceuticals Inc., 1 8582612934, cgavilanes@ACADIA-Pharm.com
Scientific contact	Chelsea Gavilanes, ACADIA Pharmaceuticals Inc., 1 8582612934, cgavilanes@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	19 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 January 2024
Global end of trial reached?	Yes
Global end of trial date	19 February 2024
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:

An independent Data and Safety Monitoring Board (DSMB) reviewed interim safety data, including data on AEs and SAEs. The DSMB was independent of the Sponsor and the Investigators and was empowered to recommend stopping the study due to safety concerns. The DSMB reviewed blinded, unblinded, or partially unblinded data, but the Sponsor and the Investigators remained blinded to the data provided to the DSMB until the official unblinding of the clinical database at the end of the study. The membership, activities, responsibilities, and frequency of meetings were described separately in a DSMB charter.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 August 2020
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: 8
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Croatia: 13
Country: Number of subjects enrolled	Bulgaria: 144
Country: Number of subjects enrolled	Czechia: 10
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Lithuania: 1
Country: Number of subjects enrolled	Argentina: 78
Country: Number of subjects enrolled	Russian Federation: 77
Country: Number of subjects enrolled	Serbia: 45
Country: Number of subjects enrolled	Ukraine: 44
Worldwide total number of subjects	453
EEA total number of subjects	209

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)	453
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

640 subjects were screened and 453 were enrolled (=randomized and treated)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

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:

two whole tablets per dose once daily at approximately the same time each day from Baseline to Week 26

Arm title	Pimavanserin

Arm description: -

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:

taken orally as two whole tablets per dose (34 mg: 2x 17 mg) once daily at approximately the same time each day from Baseline until Week 26

Number of subjects in period 1	Placebo	Pimavanserin
Started	226	227
Completed	188	195
Not completed	38	32
Consent withdrawn by subject	11	10
Adverse event, non-fatal	14	6

Non-compliance with study drug	2	3
Use of prohibited medication	-	2
Lost to follow-up	1	-
Geopolitical Conflict (Any Other)	-	2
Lack of efficacy	1	-
Protocol deviation	9	6
Lack of efficacy	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Pimavanserin
Reporting group description: -	

Reporting group values	Placebo	Pimavanserin	Total
Number of subjects	226	227	453
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	226	227	453
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	37.5	36.3	
standard deviation	± 9.78	± 9.61	-
Gender categorical Units: Subjects			
Female	90	95	185
Male	136	132	268
Race Units: Subjects			
White	224	225	449
American Indian or Alaska Native	1	0	1
Other	1	2	3
NSA-16 Total score			
Negative Symptom Assessment-16 (NSA-16) The NSA 16 is a 16 item scale that can be completed in approximately 20 to 30 minutes for most subjects but may take longer (i.e., based on effort and/or response of the subject). The NSA 16 has been validated for the assessment of the negative symptoms of schizophrenia and assesses five domains of negative symptoms: (1) communication, (2) emotion/affect, (3) social involvement, (4) motivation, and (5) retardation.			
Units: score			
arithmetic mean	60.8	61.3	
standard deviation	± 7.86	± 8.04	-
CGI-SCH S of negative symptoms score			
Clinical Global Impression of Schizophrenia Scale-Severity (CGI-SCH S) is a clinician rated, 7 point scale that is designed to evaluate positive, negative, depressive, and cognitive symptoms as well as overall severity in schizophrenia. For the purposes of this study, only the negative symptoms were evaluated.			
Units: Score			

arithmetic mean	4.8	4.8	
standard deviation	± 0.57	± 0.60	-

Subject analysis sets	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Randomized and treated with at least one dose of study drug	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Randomized and treated with at least one dose of study drug, and have both a Baseline and at least one postbaseline NSA-16 total score	

Reporting group values	Safety Analysis Set	Full Analysis Set	
Number of subjects	453	446	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	453	446	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	36.9	36.9	
standard deviation	± 9.71	± 9.76	
Gender categorical Units: Subjects			
Female	185	181	
Male	268	265	
Race Units: Subjects			
White	449	442	
American Indian or Alaska Native	1	1	
Other	3	3	
NSA-16 Total score			
Negative Symptom Assessment-16 (NSA-16) The NSA 16 is a 16 item scale that can be completed in approximately 20 to 30 minutes for most subjects but may take longer (i.e., based on effort and/or response of the subject). The NSA 16 has been validated for the assessment of the negative symptoms of schizophrenia and assesses five domains of negative symptoms: (1) communication, (2) emotion/affect, (3) social involvement, (4) motivation, and (5) retardation.			
Units: score			
arithmetic mean	61.1	61.1	

standard deviation	± 7.95	± 7.98	
CGI-SCH S of negative symptoms score			
Clinical Global Impression of Schizophrenia Scale-Severity (CGI-SCH S) is a clinician rated, 7 point scale that is designed to evaluate positive, negative, depressive, and cognitive symptoms as well as overall severity in schizophrenia. For the purposes of this study, only the negative symptoms were evaluated.			
Units: Score			
arithmetic mean	4.8	4.8	
standard deviation	± 0.58	± 0.59	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Pimavanserin
Reporting group description: -	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Randomized and treated with at least one dose of study drug	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Randomized and treated with at least one dose of study drug, and have both a Baseline and at least one postbaseline NSA-16 total score	

Primary: Change From Baseline to Week 26 in NSA-16 Total Score

End point title	Change From Baseline to Week 26 in NSA-16 Total Score
End point description:	
End point type	Primary
End point timeframe:	
Baseline to Week 26 of treatment	

End point values	Placebo	Pimavanserin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	224		
Units: score				
arithmetic mean (standard deviation)	-11.09 (± 9.18)	-12.14 (± 10.29)		

Statistical analyses

Statistical analysis title	Difference between treatments
Statistical analysis description:	
Difference between LSM changes for adjunctive pimavanserin and adjunctive placebo (pimavanserin – placebo) at the specified visit from MMRM analysis.	
Comparison groups	Placebo v Pimavanserin
Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4825 [1]
Method	Mixed models analysis

Notes:
[1] - Two-sided p-value for treatment difference at Week 26 from MMRM analysis

Secondary: Change From Baseline to Week 26 in the CGI-SCH-S Score

End point title	Change From Baseline to Week 26 in the CGI-SCH-S Score

End point description:

End point type	Secondary

End point timeframe:
Baseline to Week 26

End point values	Placebo	Pimavanserin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	224		
Units: score				
arithmetic mean (standard deviation)	-087 (± 0.92)	-0.88 (± 0.91)		

Statistical analyses

Statistical analysis title	Difference between treatments
Comparison groups	Placebo v Pimavanserin
Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8872 [2]
Method	Mixed models analysis

Notes:
[2] - Two-sided p-value for treatment difference at Week 26 from MMRM analysis

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 05 August 2020 - 19 February 2024	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0
Reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo group	
Reporting group title	Pimavanserin
Reporting group description: Pimavanserin 34 mg daily	

Serious adverse events	Placebo	Pimavanserin	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 226 (3.10%)	2 / 227 (0.88%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 226 (0.44%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	4 / 226 (1.77%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 226 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	0 / 226 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritability			
subjects affected / exposed	1 / 226 (0.44%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 226 (0.00%)	1 / 227 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 226 (0.44%)	0 / 227 (0.00%)	
occurrences causally related to treatment / all	0 / 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	Placebo	Pimavanserin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 226 (7.08%)	9 / 227 (3.96%)	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 226 (7.08%)	9 / 227 (3.96%)	
occurrences (all)	18	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 January 2020	change the dosing regimen to a fixed 34 mg dose and adjust the efficacy endpoints in comparison to the original protocol
07 August 2020	increase the sample size, number of sites, and country number
05 October 2022	adjust the Screening Period from 4 to 6 weeks to up to 6 weeks. The minimum period of 28 days was not required, as inclusion criteria #17 ensured that subjects were stable prior to Screening and inclusion in the study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported