Clinical trial results:
A Phase 3b, Multicenter, Randomized, Double-blind, Placebo-controlled, Safety Study of Pimavanserin Therapy in Adult and Elderly Subjects With Neuropsychiatric Symptoms Related to Neurodegenerative Disease

Summary

EudraCT number	2017-003536-36
Trial protocol	CZ BG RO
Global end of trial date	06 May 2022

Results information

Result version number	v1 (current)
This version publication date	19 March 2025
First version publication date	19 March 2025

Trial information

Trial identification

Sponsor protocol code	ACP-103-046

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03575052
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 58261 2897, medicalinformation@acadia-pharm.com
Scientific contact	Sr. Dir. Medical Information and Medical Communications, Acadia Pharmaceuticals Inc., +1 58261 2897, 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	06 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 May 2022
Global end of trial reached?	Yes
Global end of trial date	06 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of pimavanserin compared to placebo in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 May 2018
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: 109
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Bulgaria: 58
Country: Number of subjects enrolled	Czechia: 38
Country: Number of subjects enrolled	Colombia: 24
Country: Number of subjects enrolled	United States: 232
Country: Number of subjects enrolled	Ukraine: 107
Country: Number of subjects enrolled	Mexico: 14
Country: Number of subjects enrolled	South Africa: 14
Country: Number of subjects enrolled	Georgia: 27
Country: Number of subjects enrolled	Russian Federation: 110
Country: Number of subjects enrolled	Serbia: 45
Worldwide total number of subjects	784
EEA total number of subjects	211

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)	118
From 65 to 84 years	628
85 years and over	38

Subject disposition

Recruitment

Recruitment details:

This was a multicenter study in adult and elderly patients with neuropsychiatric symptoms related to neurodegenerative disease.

Pre-assignment

Screening details:

During the screening period, patients were assessed for eligibility; prohibited medications were discontinued. Investigators were not to withdraw a prohibited medication for the purpose of enrolling patients. Medications were discontinued only when it was deemed clinically appropriate and in consultation with the treating physician.

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, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Pimavanserin matching placebo (administered as 2 capsules) once daily

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

Dosage and administration details:

Once daily

Arm title	Pimavanserin

Arm description:

Pimavanserin 34 mg (administered as 2 x 17 mg capsules) once daily

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

Dosage and administration details:

Once daily

Number of subjects in period 1	Placebo	Pimavanserin
Started	392	392
Completed	367	363
Not completed	25	29
Adverse event, serious fatal	2	1
Consent withdrawn by subject	5	6
Physician decision	1	-
Study drug noncompliance	1	2
Adverse event, non-fatal	6	10
Lost to follow-up	3	-
Not further specified	5	7
Lack of efficacy	2	1
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Pimavanserin matching placebo (administered as 2 capsules) once daily	
Reporting group title	Pimavanserin
Reporting group description:	
Pimavanserin 34 mg (administered as 2 x 17 mg capsules) once daily	

Reporting group values	Placebo	Pimavanserin	Total
Number of subjects	392	392	784
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	72.1	72.7	
standard deviation	± 7.13	± 6.91	-
Gender categorical			
Units: Subjects			
Female	213	240	453
Male	179	152	331

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Pimavanserin matching placebo (administered as 2 capsules) once daily	
Reporting group title	Pimavanserin
Reporting group description:	
Pimavanserin 34 mg (administered as 2 x 17 mg capsules) once daily	

Primary: Treatment-emergent Adverse Events (TEAEs)

End point title	Treatment-emergent Adverse Events (TEAEs)[1]
End point description:	
Number (%) of patients with treatment-emergent AEs	
End point type	Primary
End point timeframe:	
Treatment Period: 8 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoint was a safety endpoint, the incidence of TEAEs. No statistical analysis was planned or performed for this endpoint.

End point values	Placebo	Pimavanserin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	392	392		
Units: Patients	115	119		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 8 in Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A)

End point title	Change From Baseline to Week 8 in Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A)
End point description:	
The ESRS is a questionnaire to assess drug induced movement disorders, including parkinsonism; the ESRS-A is an accepted modified form of the original ESRS. The ESRS-A consists of 4 subscales and 4 clinical global impression movement severity scales of Parkinsonism, dyskinesia, dystonia, and akathisia. The Parkinsonism scale consists of 10 items, the dyskenesia subscale of 6 items, the dystonia subscale of 6 items, and the akathisia subscale of 2 items. Each item is scored on a 6-point scale from 0 (absent) to 5 (extreme). The ESRS-A total score is the sum of the 24 item scores with a possible range of 0 to 120. Higher scores denote more severe drug-induced movement disorders.	
End point type	Secondary
End point timeframe:	
Treatment Period: 8 weeks	

End point values	Placebo	Pimavanserin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	392	392		
Units: Score on a scale				
least squares mean (standard error)	-0.6 (± 0.19)	-0.5 (± 0.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 8 in Mini-Mental State Examination (MMSE)

End point title	Change From Baseline to Week 8 in Mini-Mental State Examination (MMSE)

End point description:

The MMSE is a 30-itemt questionnaire to quantitatively assess cognition, focusing on questions related to time and place of testing, repeating lists of words, arithmetic, language use and comprehension, and copying a drawing. Each of the 30 items has 2 possible values of 0 (incorrect) or 1 (correct). The MMSE total score is derived as the sum of the 30 item scores; thus, it can range from 0 to 30. Lower scores indicate more severe cognitive impairment.

End point type	Secondary

End point timeframe:

Treatment Period: 8 weeks

End point values	Placebo	Pimavanserin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	392	392		
Units: Score on a scale				
least squares mean (standard error)	1.2 (± 0.15)	1.3 (± 0.15)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment period (8 weeks) and follow-up period (30 days): total of approximately 15 weeks	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Pimavanserin matching placebo (administered as 2 capsules) once daily	
Reporting group title	Pimavanserin
Reporting group description:	
Pimavanserin 34 mg (administered as 2 x 17 mg capsules) once daily	

Serious adverse events	Placebo	Pimavanserin	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 392 (1.53%)	8 / 392 (2.04%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	2	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic neoplasm			
subjects affected / exposed	1 / 392 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 392 (0.26%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Femure fracture			
subjects affected / exposed	0 / 392 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			

subjects affected / exposed	1 / 392 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 392 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 392 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 392 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 392 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 392 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 392 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 392 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Subarachnoid haemorrhage			
subjects affected / exposed	0 / 392 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Syncope			
subjects affected / exposed	0 / 392 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 392 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 392 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 392 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 392 (0.26%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 392 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	0 / 392 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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 / 392 (4.08%)	25 / 392 (6.38%)	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	16 / 392 (4.08%)	25 / 392 (6.38%)	
occurrences (all)	16	26	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2017	-Study phase was changed from Phase 4 to Phase 3b. -Estimated number of sites was increased from 75 to 150 and estimated number of patients was increased from 532 to 760 randomised. -Text was added to update MMRM model description for EQ-5D-5L endpoint. -Extrapyramidal Symptom Rating Scale–Abbreviated was removed from the safety follow-up visit. -Probabilities of observing AEs were adjusted based on the new sample size. -Text stating overdose of study drug without signs or symptoms would not be considered an AE was removed.
05 December 2017	-Assessment of safety and tolerability described by EPS and cognition was added as secondary objective. As a result of this addition, ESRS-A and MMSE were switched from primary to secondary endpoints. -Assessment of safety and tolerability of pimavanserin as described by suicidality. was added as exploratory objective. Accordingly, C-SSRS and GCAS were switched from primary to exploratory endpoints. -Laboratory and ECG results were removed as primary endpoints but retained as safety assessments. -Repetition of ECGs at Screening or Baseline was allowed. -Sleep Disorders Inventory was added as an exploratory endpoint (Baseline, Weeks 4 and 8/EOT). -Estimated number of sites was revised to 80; estimated number of patients was decreased to 300 randomised. The probabilities of observing AEs was adjusted based on the new sample size. -Inclusion/exclusion criteria were revised to: exclude pregnant or breast feeding patients; exclude patients with severe or medically significant impairment of hepatic or renal function. Patients with stroke within 3 months before Visit 1 or history of central nervous system neoplasm or unexplained syncope were not allowed. Retesting of patients testing positive for amphetamines was allowed. -Statistical details were added, defining MMRM for change from Baseline in MMSE and ESRS-A scores and ANCOVA for EQ-5D-5L. -Mini-Mental State Examination was added to all scheduled visits; EQ-5D-5L was added to Baseline and Week 8/EOT -Pregnancy test was added at Week 8 or EOT visit. -Urine toxicity screen was removed at Baseline. -CGI–S and ESRS-A were added to unscheduled visits. CGI-I was added at Weeks 1, 2, 4, 6, and 8/EOT. -Magnesium testing was added at Screening; TSH and free T4 testing were limited to Screening.
30 January 2018	-Specified that a serum pregnancy test should be conducted at Visit 1, and urine pregnancy tests at all subsequent visits. -Clarified process for repeating if ECGs.

01 May 2018	-Changed indication from psychosis symptoms to neuropsychiatric symptoms. Consequently, inclusion criteria related to NPI were changed to indicate that patients were required to have at least one individual domain score greater than or equal to 4. -Inclusion criteria were revised related to reliability of the designated study partner/caregiver, the discontinuation of cholinesterase inhibitor or memantine prior to Baseline, and that MRI could be conducted instead of CT at Screening. -Exclusion criteria were revised to exclude patients with implantable cardiac defibrillator and those with history of HIV or hepatitis C infection. -Exclusion criteria were revised regarding QTcF levels allowed for patients on citalopram, escitalopram, or venlafaxine, regarding retesting of patients with prolonged QTcF, and regarding heart rate assessment in patients with bradycardia. -Clinical laboratory tests were added i.e. VLDL, absolute neutrophil count, and leukocyte esterase.
09 January 2019	-Clarified timing of safety follow-up and definition of screening period -Extended period of AE recording for patients who rolled over into an open-label extension study -Updated TEAE definition -Specified management of cases of significant undercompliance (defined as <80% compliance) -Added temperature to vital sign measurements -Clarified description of ECG parameters, added RR interval -Clarified that unblinded interim analyses were allowed for patients who had exited the study to support safety evaluations for regulatory submissions -Clarified that lack of Medical Monitor contact does not preclude the Investigator from unblinding the patient. -Modified table of prohibited and restricted medications to better define anticholinergics, to more clearly define the washout period for anticonvulsants and mood stabilisers, and to prohibit use of methadone
25 July 2019	-Number of study sites was updated to about 100; number of patients was updated to about 750. -Exclusion criteria were updated to exclude patients with aneurysm with a risk of rupture above threshold. -Probabilities of observing AEs were adjusted based on the new sample size. -Clarified timing of safety follow-up. -Added definitions of prior and concomitant medications. -Added a newsection describing Acadia’s quality risk management policy. -Clarified the requirements for the use of prohibited and restricted medications for esketamine and benzodiazepine use.

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.

Not applicable

Notes: