



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 Extrapyrimal Symptom Rating Scale-Abbreviated (ESRS-A)

| | |
|---|--|
| End point title | Change From Baseline to Week 8 in Extrapyrimal 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 dyskinesia 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 (\pm 0.19) | -0.5 (\pm 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-item 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 (\pm 0.15) | 1.3 (\pm 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 | <ul style="list-style-type: none">-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 | <ul style="list-style-type: none">-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 | <ul style="list-style-type: none">-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 | <ul style="list-style-type: none"> -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 | <ul style="list-style-type: none"> -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 | <ul style="list-style-type: none"> -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 new section 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: