# Clinical trial results:
# A Phase 1, Open Label, Multiple Ascending Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Pimavanserin in Adolescents with Psychiatric Disorders

## Summary

| | |
|---|---|
| EudraCT number | 2018-001064-30 |
| Trial protocol | BG |
| Global end of trial date | 26 September 2019 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 21 August 2022 |
| First version publication date | 21 August 2022 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | ACP-103-050 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| 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) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-001688-PIP03-16 |
| 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? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 11 May 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 September 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 September 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetics (PK) and safety and tolerability following multiple doses of pimavanserin (10, 20, or 34 mg) in adolescents with psychiatric disorders

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 17 July 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Bulgaria: 10 |
| Country: Number of subjects enrolled | Russian Federation: 2 |
| Country: Number of subjects enrolled | United States: 22 |
| Worldwide total number of subjects | 34 |
| EEA total number of subjects | 10 |

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) | 34 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted as a multicenter, open-label, multiple ascending dose (10, 20, or 34 mg) study in adolescents with psychiatric disorders. Subjects who prematurely discontinued from the study for any reason could have been replaced to ensure the minimum subject requirements were met for each age subset.

### Pre-assignment

Screening details:

During the Screening period, subjects were assessed for study eligibility. The Screening period was 1 to 28 days in duration.

### Period 1

| | |
|---|---|
| Period 1 title | Overall study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Pimavanserin 10 mg |

Arm description:

Pimavanserin, 10 mg (1×10 mg tablets), once daily as a single oral dose

| | |
|---|---|
| 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:

Pimavanserin, tablet, once daily as a single oral dose

| | |
|---|---|
| **Arm title** | Pimavanserin 20 mg |

Arm description:

Pimavanserin, 20 mg (2×10 mg tablets), once daily as a single oral dose

| | |
|---|---|
| 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:

Pimavanserin, tablet, once daily as a single oral dose

| | |
|---|---|
| **Arm title** | Pimavanserin 34 mg |

Arm description:

Pimavanserin, 34 mg (2×17 mg tablets), once daily as a single oral dose

| | |
|---|---|
| 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:

Pimavanserin, tablet, once daily as a single oral dose

| **Number of subjects in period 1** | Pimavanserin 10 mg | Pimavanserin 20 mg | Pimavanserin 34 mg |
|---|---|---|---|
| Started | 12 | 10 | 12 |
| Completed | 10 | 10 | 11 |
| Not completed | 2 | 0 | 1 |
| Physician decision | 1 | - | - |
| Consent withdrawn by subject or parent/guardian | 1 | - | - |
| Protocol deviation | - | - | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Pimavanserin 10 mg |
| Reporting group description: | |
| Pimavanserin, 10 mg (1×10 mg tablets), once daily as a single oral dose | |
| Reporting group title | Pimavanserin 20 mg |
| Reporting group description: | |
| Pimavanserin, 20 mg (2×10 mg tablets), once daily as a single oral dose | |
| Reporting group title | Pimavanserin 34 mg |
| Reporting group description: | |
| Pimavanserin, 34 mg (2×17 mg tablets), once daily as a single oral dose | |

| Reporting group values | Pimavanserin 10 mg | Pimavanserin 20 mg | Pimavanserin 34 mg |
|---|---|---|---|
| Number of subjects | 12 | 10 | 12 |
| Age categorical | | | |
| Safety Analysis Set | | | |
| 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) | 12 | 10 | 12 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 4 | 5 | 5 |
| Male | 8 | 5 | 7 |
| Age, Study-Specific Categories<br>Units: Subjects | | | |
| 13 to <15 years | 6 | 4 | 4 |
| 15 to <18 years | 6 | 6 | 8 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 34 | | |
| Age categorical | | | |
| Safety Analysis Set | | | |
| 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) | 34 | | |
| Adults (18-64 years) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 14 | | |
| Male | 20 | | |
| Age, Study-Specific Categories<br>Units: Subjects | | | |
| 13 to <15 years | 14 | | |
| 15 to <18 years | 20 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Pimavanserin 10 mg |
| Reporting group description: | |
| Pimavanserin, 10 mg (1×10 mg tablets), once daily as a single oral dose | |
| Reporting group title | Pimavanserin 20 mg |
| Reporting group description: | |
| Pimavanserin, 20 mg (2×10 mg tablets), once daily as a single oral dose | |
| Reporting group title | Pimavanserin 34 mg |
| Reporting group description: | |
| Pimavanserin, 34 mg (2×17 mg tablets), once daily as a single oral dose | |

### Primary: Maximum plasma concentration at steady state (Cmax,ss)

| | |
|---|---|
| End point title | Maximum plasma concentration at steady state (Cmax,ss)[1] |
| End point description: | |
| Maximum observed plasma concentration of pimavanserin at steady state | |
| End point type | Primary |
| End point timeframe: | |
| Steady state profile blood samples were collected on Day 20 predose (within 30 min prior to dosing) and 1, 2, 4, 6, 9, 12, 16, and 24 h after last dose of pimavanserin administration. | |

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: No inferential statistical analyses were planned or performed for this Phase I, multiple-ascending dose study.

| End point values | Pimavanserin 10 mg | Pimavanserin 20 mg | Pimavanserin 34 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 10 | 7 | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Overall | 17.8 (± 4.14) | 43.2 (± 15.0) | 80.5 (± 24.2) | |

### Statistical analyses

No statistical analyses for this end point

### Primary: Time to maximum plasma concentration at steady state (Tmax,ss)

| | |
|---|---|
| End point title | Time to maximum plasma concentration at steady state (Tmax,ss)[2] |
| End point description: | |
| Time to maximum plasma concentration of pimavanserin at steady state | |
| End point type | Primary |
| End point timeframe: | |
| Steady state profile blood samples were collected on Day 20 predose (within 30 min prior to dosing) and 1, 2, 4, 6, 9, 12, 16, and 24 h after last dose of pimavanserin administration. | |

Notes:

[2] - 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: No inferential statistical analyses were planned or performed for this Phase I, multiple-ascending dose study.

| **End point values** | Pimavanserin 10 mg | Pimavanserin 20 mg | Pimavanserin 34 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 10 | 7 | |
| Units: hr | | | | |
| median (full range (min-max)) | | | | |
| Overall | 6.00 (4.00 to 12.0) | 5.98 (4.00 to 12.0) | 9.00 (2.00 to 12.0) | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Area under the concentration-time curve during any dosing interval at steady state (AUCτ)

| End point title | Area under the concentration-time curve during any dosing interval at steady state (AUCτ)[3] |
|---|---|

End point description:

Area under the concentration-time curve of pimavanserin during any dosing interval at steady state

| End point type | Primary |
|---|---|

End point timeframe:

Steady state profile blood samples were collected on Day 20 predose (within 30 min prior to dosing) and 1, 2, 4, 6, 9, 12, 16, and 24 h after last dose of pimavanserin administration.

Notes:

[3] - 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: No inferential statistical analyses were planned or performed for this Phase I, multiple-ascending dose study.

| **End point values** | Pimavanserin 10 mg | Pimavanserin 20 mg | Pimavanserin 34 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 10 | 7 | |
| Units: ng×hr/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Overall | 348 (± 92.3) | 812 (± 297) | 1683 (± 538) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Accumulation ratio based on Cmax (Rac)

| End point title | Accumulation ratio based on Cmax (Rac) |
|---|---|

End point description:

The accumulation of pimavanserin was evaluated based on the Cmax,ss of Day 20 (multiple dose) vs the Cmax of Day 1 (single dose), for each pimavanserin dose, using descriptive statistics.

| End point type | Secondary |
|---|---|

End point timeframe:

The 24-hour PK sampling was done on Day 1 through 2 and Day 20 through 21. Steady state profile blood samples were collected on Day 20 predose (within 30 min before dosing) and 1, 2, 4, 6, 9, 12, 16, and 24 h after last dose of pimavanserin administrated.

| **End point values** | Pimavanserin 10 mg | Pimavanserin 20 mg | Pimavanserin 34 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 10 | 7 | |
| Units: Cmax | | | | |
| arithmetic mean (standard deviation) | | | | |
| Overall | 3.13 (± 0.852) | 3.73 (± 0.695) | 4.15 (± 1.29) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Accumulation ratio based on AUC (Rac)

| End point title | Accumulation ratio based on AUC (Rac) |
|---|---|

End point description:

The accumulation of pimavanserin was evaluated based on the AUCτ on Day 20 (multiple dose) vs the AUC0-24 ofnDay 1 (single dose), for each pimavanserin dose, using descriptive statistics.

| End point type | Secondary |
|---|---|

End point timeframe:

The 24-hour PK sampling was done on Day 1 through 2 and Day 20 through 21. Steady state profile blood samples were collected on Day 20 predose (within 30 min before dosing) and 1, 2, 4, 6, 9, 12, 16, and 24 h after last dose of pimavanserin administrated.

| **End point values** | Pimavanserin 10 mg | Pimavanserin 20 mg | Pimavanserin 34 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 10 | 7 | |
| Units: AUCτ | | | | |
| arithmetic mean (standard deviation) | | | | |
| Overall | 3.59 (± 1.07) | 4.15 (± 0.726) | 4.88 (± 1.66) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Apparent systemic clearance following oral administration (CL/F)

| End point title | Apparent systemic clearance following oral administration (CL/F) |
|---|---|

End point description:

Apparent systemic clearance following oral administration of pimavanserin determined on Day 20 (steady state)

| End point type | Secondary |
|---|---|

End point timeframe:

Steady state profile blood samples were collected on Day 20 predose (within 30 min before dosing) and 1, 2, 4, 6, 9, 12, 16, and 24 h after last dose of pimavanserin administrated.

| End point values | Pimavanserin 10 mg | Pimavanserin 20 mg | Pimavanserin 34 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 10 | 10 | 7 | |
| Units: L/hr | | | | |
| arithmetic mean (standard deviation) | | | | |
| Overall | 30.8 (± 8.93) | 27.6 (± 9.45) | 22.4 (± 8.63) | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: Adverse events were recorded from the time informed assent/consent was obtained through the Day 50 follow-up visit. | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.0 |

| Reporting groups | |
|---|---|
| Reporting group title | Pimavanserin 10 mg |
| Reporting group description: Pimavanserin, 10 mg (1×10 mg tablets), once daily as a single oral dose | |
| Reporting group title | Pimavanserin 20 mg |
| Reporting group description: Pimavanserin, 20 mg (2×10 mg tablets), once daily as a single oral dose | |
| Reporting group title | Pimavanserin 34 mg |
| Reporting group description: Pimavanserin, 34 mg (2×17 mg tablets), once daily as a single oral dose | |

| Serious adverse events | Pimavanserin 10 mg | Pimavanserin 20 mg | Pimavanserin 34 mg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 0 / 12 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

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

| Non-serious adverse events | Pimavanserin 10 mg | Pimavanserin 20 mg | Pimavanserin 34 mg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 12 (75.00%) | 7 / 10 (70.00%) | 4 / 12 (33.33%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood prolactin increased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Weight increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 2 / 10 (20.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 4 | 2 | 0 |
| Sedation | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 3 / 10 (30.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 1 | 6 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Psychiatric disorders | | | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Renal and urinary disorders | | | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Endocrine disorders | | | |
| Hyperprolactinaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 18 July 2018 | - Clarified the descriptions of inpatient and outpatient study procedures<br>- Clarified description of prohibited and restricted medications<br>- Clarified repeat ECG procedure<br>- Revised exclusion criteria to also exclude new onset diabetes<br>- Clarified procedure for screening thyroid function test<br>- Clarified definition of TEAE (to include AEs up to 30 days after the last dose of study drug)<br>- Updated analysis of dose proportionality and analysis of C-SSRS<br>- Added UKU-SERS assessment on Day 28<br>- Corrected postdose fasting period from 4 to 2 h and clarified that fluids were not allowed during fasting<br>- Corrected time window for predose and postdose PK sampling, vital signs, and ECG |
| 15 October 2018 | - Updated final follow-up visit from 28 to 30 days after last dose<br>- Clarified fasting requirement on Day 1 and Day 20 of PK sampling<br>- Updated semisupine to resting position (sitting or supine)<br>- Corrected lower range of pulse rate from <60 to <50 bpm and that pulse rate was to be measured by ECG<br>- Corrected lower range of hemoglobin value and provided values by sex (<11.3 g/dL for females and <11.0 g/dL for males)<br>- Updated HbA1c value (HbA1c >6.5%) to match for Type 2 diabetes<br>- Allowed for a repeat set of triplicate ECGs<br>- Revised age from a fixed effect to a covariate for PK analysis<br>- Clarified visits and requirements for complete UDS<br>- Clarified that UKU-SERS assessment was to be performed after dosing |
| 05 November 2018 | Clarified exclusion criteria related to heart rate and ECGs |
| 05 March 2019 | - Correctied information on amount of blood drawn for safety sampling and total blood volume<br>- Clarified statistical planning for PK analyses<br>- Updated sponsor address |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported