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 Units: Subjects			
Female	4	5	5
Male	8	5	7
Age, Study-Specific Categories 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 Units: Subjects			
Female	14		
Male	20		
Age, Study-Specific Categories 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 - Clarified description of prohibited and restricted medications - Clarified repeat ECG procedure - Revised exclusion criteria to also exclude new onset diabetes - Clarified procedure for screening thyroid function test - Clarified definition of TEAE (to include AEs up to 30 days after the last dose of study drug) - Updated analysis of dose proportionality and analysis of C-SSRS - Added UKU-SERS assessment on Day 28 - Corrected postdose fasting period from 4 to 2 h and clarified that fluids were not allowed during fasting - 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 - Clarified fasting requirement on Day 1 and Day 20 of PK sampling - Updated semisupine to resting position (sitting or supine) - Corrected lower range of pulse rate from <60 to <50 bpm and that pulse rate was to be measured by ECG - Corrected lower range of hemoglobin value and provided values by sex (<11.3 g/dL for females and <11.0 g/dL for males) - Updated HbA1c value (HbA1c >6.5%) to match for Type 2 diabetes - Allowed for a repeat set of triplicate ECGs - Revised age from a fixed effect to a covariate for PK analysis - Clarified visits and requirements for complete UDS - 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 - Clarified statistical planning for PK analyses - Updated sponsor address

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported