Clinical trial results:
A 52-Week Open-Label Extension Study of Pimavanserin in Subjects With Major Depressive Disorder and Inadequate Response to Antidepressant Treatment

Summary

EudraCT number	2018-003252-20
Trial protocol	GB SK PL FI
Global end of trial date	22 February 2021

Results information

Result version number	v1 (current)
This version publication date	08 March 2022
First version publication date	08 March 2022

Trial information

Trial identification

Sponsor protocol code	ACP-103-055

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04000009
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, +1 858 261 2897, medicalinformation@acadia-pharm.com
Scientific contact	Sr. Dir. Medical Information and Medical Communications, ACADIA Pharmaceuticals Inc, +1 858 261 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	22 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2021
Global end of trial reached?	Yes
Global end of trial date	22 February 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of long-term pimavanserin treatment in subjects with major depressive disorder and inadequate response to antidepressant treatment

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 June 2019
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	Poland: 16
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	Russian Federation: 26
Country: Number of subjects enrolled	Serbia: 13
Country: Number of subjects enrolled	South Africa: 1
Country: Number of subjects enrolled	Ukraine: 26
Country: Number of subjects enrolled	United States: 111
Worldwide total number of subjects	235
EEA total number of subjects	31

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)	218
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study recruited patients that had completed a previous study of pimavanserin, i.e. study ACP-103-054 or ACP-103-059. It was planned to enroll about 420 patients.
The study was terminated early by the Sponsor for business reasons due to the COVID-19 pandemic; there were no safety concerns contributing to study termination.

Pre-assignment

Screening details:

During the screening period, subjects were assessed for study eligibility and prohibited medications were discontinued when medically appropriate.

Period 1

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

Arms

Arm title	Pimavanserin

Arm description:

Pimavanserin 34 mg (administered as 2 x 17 mg pimavanserin tablets) once daily, for 52 weeks

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 34 mg (administered as 2 x 17 mg pimavanserin tablets) taken once daily, for 52 weeks

Number of subjects in period 1	Pimavanserin
Started	235
Completed	70
Not completed	165
Physician decision	1
Consent withdrawn by subject	22
Adverse event, non-fatal	13
Pregnancy	1
Study terminated by sponsor	98
Noncompliance with study drug	4
Use of prohibited medication	3
Lost to follow-up	8
Not further specified	8

Lack of efficacy	7

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	235	235	
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	45.5		
standard deviation	± 13.90	-	
Gender categorical Units: Subjects			
Female	165	165	
Male	70	70	

End points

End points reporting groups

Reporting group title	Pimavanserin
Reporting group description:	
Pimavanserin 34 mg (administered as 2 x 17 mg pimavanserin tablets) once daily, for 52 weeks	

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:	
52 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: This was a single-arm study. Inferential testing was neither planned nor performed.

End point values	Pimavanserin			
Subject group type	Reporting group			
Number of subjects analysed	235			
Units: Patients	137			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 52 weeks	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Pimavanserin
Reporting group description: Pimavanserin 34 mg (administered as 2 x 17 mg pimavanserin tablets) once daily, for 52 weeks	

Serious adverse events	Pimavanserin		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 235 (2.13%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholangiocarcinoma			
subjects affected / exposed	1 / 235 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diverticular perforation			
subjects affected / exposed	1 / 235 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal obstruction			
subjects affected / exposed	1 / 235 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Nasal septum deviation			

subjects affected / exposed	1 / 235 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 235 (0.43%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pimavanserin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 235 (29.36%)		
Investigations			
Weight increased			
subjects affected / exposed	14 / 235 (5.96%)		
occurrences (all)	14		
Nervous system disorders			
Headache			
subjects affected / exposed	29 / 235 (12.34%)		
occurrences (all)	39		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 235 (5.11%)		
occurrences (all)	13		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 235 (6.38%)		
occurrences (all)	17		
Urinary tract infection			
subjects affected / exposed	12 / 235 (5.11%)		
occurrences (all)	12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2018	Key changes included: - Allowed inclusion of patients beyond elderly population - Removed cognition and replaced quality of life with functional impairment and sexual functioning as exploratory assessments - Removed Mini-Mental Sate Examination score as exploratory safety endpoint - Removed EQ-5D as exploratory efficacy endpoint; added CSFQ-14 and KSS score as exploratory efficacy endpoints - Increased planned patient number from 290 to 420 by adding rollover patients from study ACP-103-059 in addition to -054 - Revised dosing to pimavanserin 34 mg only; removed dose adjustment between 20 and 34 mg pimavanserin - Excluded patients with comorbid neurodegenerative disorders - Adapted several study procedures/timelines to align with procedures/timelines in the rollover studies 054/059 - Removed rescue medication procedures
18 March 2019	- Removed abstinence as acceptable contraception method - Implemented less restrictive definition of suicidality
12 November 2019	Key changes included: - Added sexual dysfunction as safety endpoint - Clarified use of background antidepressants in the study - Clarified barrier methods of contraception - Clarified the assessment of heart rate for patient eligibility - Replaced BMI upper bound criterion for patient eligibility with weight increase of ≥7% as criterion - Clarified assessment of background antidepressant adherence - Clarified follow-up procedures for discontinued patients - Tightened restrictions on controlled substances - Specified randomisation in error as major protocol deviation - Added ketamine and esketamine to the list of prohibited antidepressants and clarified timeframe for stable dosing of these drugs
11 August 2020	Key changes included: - Added specifications for changes due to COVID-19 pandemic: visits performed remotely; use of a 6-lead ECG device at home; home delivery of study drug; study conduct, exploratory efficacy assessments, safety assessments, and unscheduled visits; COVID-19 relatedness of concomitant medications; relationship of selected AEs to COVID-19; protocol deviations related to COVID-19; remote monitoring of study sites due to travel/ visiting restrictions caused by COVID-19 pandemic; return of unused study drug and packaging when site staff visited patient's home - Allowed for interim analyses, if required for regulatory reporting

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.

This study was terminated early by the Sponsor for business reasons due to the COVID-19 pandemic; there were no safety concerns contributing to study termination. Patients were discontinued from the study and completed safety follow-up procedures.

Notes: