Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Adjunctive Pimavanserin in Subjects With Major Depressive Disorder and Inadequate Response to Antidepressant Treatment

Summary

EudraCT number	2018-003251-37
Trial protocol	GB SK PL FI
Global end of trial date	21 June 2020

Results information

Result version number	v1 (current)
This version publication date	07 July 2021
First version publication date	07 July 2021

Trial information

Trial identification

Sponsor protocol code	ACP-103-054

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03999918
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., 001 858 2612897, medicalinformation@acadia-pharm.com
Scientific contact	Sr. Dir. Medical Information and Medical Communications, ACADIA Pharmaceuticals Inc., 001 858 2612897, 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	30 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 April 2020
Global end of trial reached?	Yes
Global end of trial date	21 June 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of adjunctive pimavanserin compared to placebo in subjects with major depressive disorder who have an inadequate response to antidepressant therapy

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 July 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: 18
Country: Number of subjects enrolled	Slovakia: 7
Country: Number of subjects enrolled	United Kingdom: 34
Country: Number of subjects enrolled	Finland: 12
Country: Number of subjects enrolled	Ukraine: 30
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Serbia: 17
Country: Number of subjects enrolled	Russian Federation: 30
Worldwide total number of subjects	150
EEA total number of subjects	37

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)	137
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was performed in patients with with major depressive disorder who had an inadequate response to antidepressant treatment

Pre-assignment

Screening details:

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

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Pimavanserin

Arm description:

Pimavanserin 34 mg administered orally as a single dose once daily

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 2×17 mg tablets, given as a single dose once daily.

Arm title	Placebo

Arm description:

Placebo tablets administered orally as a single oral dose once daily

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

Dosage and administration details:

Placebo was given as two tablets (size- and colour-matched to pimavanserin tablets) as a single dose once daily

Number of subjects in period 1	Pimavanserin	Placebo
Started	74	76
Completed	69	71
Not completed	5	5
Consent withdrawn by subject	2	2
Adverse event, non-fatal	-	1
COVID-19 quarantine measure	2	-
Protocol deviation	1	1
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Pimavanserin
Reporting group description:	
Pimavanserin 34 mg administered orally as a single dose once daily	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets administered orally as a single oral dose once daily	

Reporting group values	Pimavanserin	Placebo	Total
Number of subjects	74	76	150
Age categorical Units: Subjects			
Adults (18-64 years)	70	67	137
From 65-84 years	4	9	13
Age continuous Units: years			
arithmetic mean	45.2	44.9	
standard deviation	± 12.40	± 14.53	-
Gender categorical Units: Subjects			
Female	47	61	108
Male	27	15	42

End points

End points reporting groups

Reporting group title	Pimavanserin
Reporting group description:	
Pimavanserin 34 mg administered orally as a single dose once daily	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets administered orally as a single oral dose once daily	

Primary: Change From Baseline in the Hamilton Depression Scale (17 Items) (HAMD-17) Total Score

End point title	Change From Baseline in the Hamilton Depression Scale (17 Items) (HAMD-17) Total Score[1]

End point description:

The HAMD-17 consists of 8 items with a score on a 3 point scale and 9 items with a score on a 5 point scale. The total score ranging from 0 to 52 will be calculated as the sum of the scores for all 17 items. Higher total scores denote more severe depression.
Prespecified inferential testing was not conducted as this trial was prematurely terminated due to business reasons as a result of COVID-19. Therefore, the number of patients with HAMD-17 assessments at BL and Week 5 is given.

End point type	Primary

End point timeframe:

Week 5

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: Prespecified inferential testing was not conducted as this trial was prematurely terminated due to business reasons as a results of COVID-19.

End point values	Pimavanserin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: Patients				
HAMD-17 assessment at BL	74	76		
HAMD-17 assessment at Week 5	70	73		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse Events (AEs) were to be documented through 30 days after the last dose in the study.	
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 orally as a single dose once daily	
Reporting group title	Placebo
Reporting group description: Placebo tablets administered orally as a single oral dose once daily	

Serious adverse events	Pimavanserin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Gastritis haemorrhagic			
subjects affected / exposed	0 / 74 (0.00%)	1 / 76 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pimavanserin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 74 (33.78%)	21 / 76 (27.63%)	
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 74 (22.97%)	18 / 76 (23.68%)	
occurrences (all)	31	29	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	6 / 74 (8.11%)	0 / 76 (0.00%)	
occurrences (all)	7	0	
Dry mouth			
subjects affected / exposed	6 / 74 (8.11%)	1 / 76 (1.32%)	
occurrences (all)	6	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 74 (4.05%)	4 / 76 (5.26%)	
occurrences (all)	3	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2018	- Expanded study from elderly to adult population - Changed timeframe of assessment for primary endpoint (HAMD-17) to change from BL to Week 5 - Revised secondary endpoints to include SDS, CGI-I, CSFQ-14, KSS, HAMD-17, and BIS-11; revised secondary endpoint analyses - Removed PK, PK/PD, exploratory objectives, endpoints, and analyses - Removed MMSE score as assessment, changed assessment timeframe for ESRS-A to Week 5 from Baseline - Decreased number of planned study sites to 40 sites - Revised timeframes for screening and double-blind periods; deleted stratification by region - Changed safety follow-up period to at least 30 days; removed DSMB - Updated duration of patient participation to 14 weeks - Removed allowance of patients with comorbid neurodegenerative disorders from inclusion criteria - Revised list of acceptable SSRI/SNRI antidepressants in inclusion criteria - Clarified procedure and inclusion criteria for repeat screening test for SSRI/SNRI - Removed exclusion criterion on Huntington's disease or motor neuron disease; revised assessment for exclusion of active suicidality - Clarified that bradycardia explained by exercise would not lead to exclusion; explained procedure for positive test for illicit drugs or cannabis and retesting criteria - Revised sample size to 266 evaluable patients - Revised statistical methods for efficacy, descriptive statistical analyses - Removed rescue medication procedures - Revised randomization methodology; removed stratified randomization by region - Eliminated collection of dementia history and neurological history - Revised timeframes for concomitant SSRI/SNRI antidepressant blood sampling - Clarified interview guides for MADRS, HAMD-17, CGI-S - Provided description for CSFQ-14 assessment, BIS-11 questionnaire - Clarified safety laboratory evaluations - Revised procedure for following a pregnancy to outcome - Updated information on prohibited, unrestricted medications
18 March 2019	- Removed the option of abstinence as an acceptable method of contraception - Implemented a less restrictive definition of suicidality in the exclusion criteria
29 October 2019	- Added new safety and tolerability endpoint (sexual dysfunction) - Extended screening period to 3-28 days - Clarified procedure for confirming subject eligibility - Clarified dosing requirements for the background antidepressant prior to SAFER interview for inclusion criteria - Clarified barrier methods of contraception for inclusion criteria - Clarified several exclusion criteria (medical conditions; cardiovascular history; viral serology; heart rate) - Added sexual dysfunction summary and shift tables to the safety analyses - Added a definition of "inadequate response" to current SSRI/SNRI antidepressant therapy - Added review of background antidepressant adherence - Added text on benefits and risks of the study - Clarified follow-up procedures for discontinued patients - Clarified prior, concomitant, and prohibited therapy and restrictions on controlled substances - Clarified major protocol deviations

21 June 2020	- Included description of changes necessitated by the COVID-19 pandemic - Added description of Study ACP-103-059 - Described impact of the COVID-19 pandemic on Studies ACP-103-054 and ACP-103-059, the study conduct during the time when screening and randomization was suspended, and the decision to combine the 2 studies for the purpose of analysis - Added COVID-19 relatedness of AEs and concomitant medications - Described the impact of the COVID-19 pandemic on efficacy and safety assessments; unscheduled visits - Added description of protocol deviation review and described handling of protocol deviations with respect to relationship to COVID-19 - Updated the statistical methods section to align with statistical Analysis plan - Changed the statistical comparison method used for both the response and remission rates

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 March 2020	In March 2020, recruitment of new patients was paused due to the emerging coronavirus disease 2019 (COVID-19) pandemic. At that point in time, about half of the planned patients had been randomized. The trial was prematurely terminated due to business reasons as a result of COVID-19. The Sponsor decided to combine this trial with the identically designed trial ACP-103-059 (conducted only in the US), with a prespecified combined statistical analysis plan. As a result, both trials were terminated and proceeded with database lock and statistical analysis of the combined trial data. No further patients were enrolled. No separate analysis for each study was performed.	-

Notes:

Limitations and caveats

None reported