Clinical trial results:
A 52-Week Open-Label Extension Study of Pimavanserin for the Treatment of Agitation and Aggression in Subjects with Alzheimer's Disease

Summary

EudraCT number	2016-001128-78
Trial protocol	ES GB
Global end of trial date	25 February 2019

Results information

Result version number	v1 (current)
This version publication date	13 March 2020
First version publication date	13 March 2020

Trial information

Trial identification

Sponsor protocol code	ACP-103-033

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03118947
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ACADIA Pharmaceuticals Inc.
Sponsor organisation address	3611 Valley Centre Drive, Ste. 300, San Diego, CA, 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	25 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 February 2019
Global end of trial reached?	Yes
Global end of trial date	25 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of pimavanserin for up to 52 weeks of treatment in patients with probable AD who have symptoms of agitation and aggression.

Protection of trial subjects:

Not applicable

Background therapy:

No specific background therapy was specified.
Patients were to continue any concomitant antidepressants, cholinesterase inhibitors, memantine, and other permitted medications at stable doses throughout the study.

Evidence for comparator:

Not applicable. This was an open-label, uncontrolled trial.

Actual start date of recruitment	22 February 2017
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	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Chile: 29
Country: Number of subjects enrolled	United States: 33
Worldwide total number of subjects	78
EEA total number of subjects	16

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)	5
From 65 to 84 years	58
85 years and over	15

Subject disposition

Recruitment

Recruitment details:

This open-label extension study included pts completing double-blind, randomised, placebo-controlled study ACP-103-032 (NCT02992132).

Pre-assignment

Screening details:

Patients from parent study ACP-103-032 who were eligible to participate in this study were consented prior to the final procedures performed for study ACP-103-032 at Week 12. The Week 12 visit of study ACP-103-032 was at the same time considered as baseline visit of study ACP-103-033.

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

Arm title	All patients

Arm description:

All patients started treatment with pimavanserin 20 mg once daily (QD). At the Week 2 visit, the dose could be increased to 34 mg QD based on the investigator's assessment of clinical response. Subsequently, the dose could be adjusted from 34 mg to 20 mg or from 20 mg to 34 mg at any visit based on clinical response.

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:

Patients started treatment with pimavanserin 20 mg once daily (QD). At the Week 2 visit, the dose could be increased to 34 mg QD based on the investigator's assessment of clinical response. Subsequently, the dose could be adjusted from 34 mg to 20 mg or from 20 mg to 34 mg at any visit based on clinical Response.

Number of subjects in period 1	All patients
Started	78
Completed	49
Not completed	29
Adverse event, serious fatal	3
Consent withdrawn by subject	3
Adverse event, non-fatal	7
Change in patient's living situation	4
Consent withdrawn by caregiver	3

Noncompliance with study drug	1
Lost to follow-up	2
Lack of efficacy	4
Protocol deviation	2

Baseline characteristics

Reporting groups	
Reporting group title	All patients

Reporting group description:

All patients started treatment with pimavanserin 20 mg once daily (QD). At the Week 2 visit, the dose could be increased to 34 mg QD based on the investigator's assessment of clinical response. Subsequently, the dose could be adjusted from 34 mg to 20 mg or from 20 mg to 34 mg at any visit based on clinical response.

Reporting group values	All patients	Total	
Number of subjects	78	78	
Age categorical Units: Subjects			
Adults (18-64 years)	5	5	
From 65-84 years	58	58	
85 years and over	15	15	
Age continuous Units: years			
arithmetic mean	76.9		
standard deviation	± 7.49	-	
Gender categorical Units: Subjects			
Female	37	37	
Male	41	41	

End points

End points reporting groups

Reporting group title	All patients

Reporting group description:

All patients started treatment with pimavanserin 20 mg once daily (QD). At the Week 2 visit, the dose could be increased to 34 mg QD based on the investigator’s assessment of clinical response. Subsequently, the dose could be adjusted from 34 mg to 20 mg or from 20 mg to 34 mg at any visit based on clinical response.

Primary: Treatment-emergent adverse events (TEAEs)

End point title	Treatment-emergent adverse events (TEAEs)[1]

End point description:

Safety and tolerability of pimavanserin after 52 weeks of treatment in patients with probable Alzheimer's disease who have symptoms of agitation and Aggression, in terms of occurrence of TEAEs

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 an open-label, uncontrolled trial. The Primary endpoint was a safety endpoint (patients with TEAEs). Inferential statistical analysis was neither planned nor performed.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: Patients				
Patients with any TEAE	53			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
52 weeks	
Adverse event reporting additional description:	
Not applicable	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	All patients

Reporting group description:

All patients started treatment with pimavanserin 20 mg once daily (QD). At the Week 2 visit, the dose could be increased to 34 mg QD based on the investigator's assessment of clinical response. Subsequently, the dose could be adjusted from 34 mg to 20 mg or from 20 mg to 34 mg at any visit based on clinical response.

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 78 (15.38%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Pelvic fracture			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Dementia Alzheimer's type			

subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Dizziness			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
Spondylolisthesis			

subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia bacteraemia			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 78 (25.64%)		
Investigations			
Weight decreased			
subjects affected / exposed	4 / 78 (5.13%)		
occurrences (all)	4		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	7 / 78 (8.97%)		
occurrences (all)	7		
Psychiatric disorders			
Agitation			
subjects affected / exposed	5 / 78 (6.41%)		
occurrences (all)	8		
Infections and infestations			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 78 (6.41%) 6		
Urinary tract infection subjects affected / exposed occurrences (all)	6 / 78 (7.69%) 9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 July 2017	- Added exclusion criteria for patients receiving skilled nursing care for any medical condition other than dementia and for patients with a Global Clinician Assessment of Suicidality (GCAS) score of 3 or 4 based on Investigator's assessment of behavior since the last assessment. - Added GCAS as a primary endpoint - Specified that the Neuropsychiatric Inventory-Clinician rating scale (NPI-C) was rated by the clinicianfor patients not able to provide reliable information (e.g. due to cognitive impairment. - Removed AEs of special interest - Added suicidal ideation and behavior as additional safety assessment
30 November 2017	The protocol of the parent study ACP-103-032 was amended on 20 Nov 2017 to stop enrollment of new patients for business reasons, not related to safety. Enrollment was stopped when 111 of approximately 432 planned patients had been randomised. Consequently, the planned patient number for this trial also had to be adjusted to 111. In addition, endpoint designations were changed i.e. TEAEs were made the primary endpoint; and previously defined secondary efficacy endpoints became exploratory endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported