Clinical trial results:
A Double-Blind, Placebo-Controlled Study to Examine the Safety and Efficacy of Pimavanserin for the Treatment of Agitation and Aggression in Alzheimer's Disease

Summary

EudraCT number	2016-001127-32
Trial protocol	ES GB
Global end of trial date	16 February 2018

Results information

Result version number	v1 (current)
This version publication date	03 March 2019
First version publication date	03 March 2019

Trial information

Trial identification

Sponsor protocol code	ACP-103-032

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02992132
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
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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	16 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 February 2018
Global end of trial reached?	Yes
Global end of trial date	16 February 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of pimavanserin treatment compared with placebo in reducing the severity of agitation and Aggression in Alzheimer's disease after 12 weeks of treatment.

Protection of trial subjects:

Not applicable

Background therapy:

Patients were allowed to continue protocol-permitted medications (e.g. antidepressants, etc.) as long as they had been stable on the same dose for at least 4 weeks prior to baseline (Day 1) and expected to remain on this dose for the duration of the study. Cholinesterase inhibitors or memantine had to be stable for at least 12 weeks before baseline and expected to remain unchanged until the patient’s final visit.

Evidence for comparator:

Not applicable

Actual start date of recruitment	07 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Chile: 34
Country: Number of subjects enrolled	United States: 57
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	France: 8
Worldwide total number of subjects	111
EEA total number of subjects	20

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	9
From 65 to 84 years	80
85 years and over	22

Subject disposition

Recruitment

Recruitment details:

The study was planned to be conducted in approximately 432 patients. For business reasons, and not related to safety, recruitment of patients was stopped after 111 patients were randomised. The last patient was randomised on 2 Nov 2017. See Limitations and Caveats.

Pre-assignment

Screening details:

The screening visit was followed by a 2- to 4-week screening period, including wash-out of antipsychotic agents prohibited during the Treatment period (exception: protocol specified agents). Patients had to be on stable doses of permitted medications for >=4 weeks before Baseline (>=12 weeks for cholinesterase Inhibitors and memantine).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo, taken as two tablets, once daily by mouth

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, taken as two tablets, once daily by mouth

Arm title	Pimavanserin 20 mg

Arm description:

Drug- pimavanserin tartrate, 20 mg, taken as two 10 mg tablets, once daily by mouth

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 20 mg, tablet, taken as two 10 mg tablets, once daily by mouth

Arm title	Pimavanserin 34 mg

Arm description:

Drug- pimavanserin tartrate, 34 mg, taken as two 17 mg tablets, once daily by mouth

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, tablet, taken as two 17 mg tablets, once daily by mouth

Number of subjects in period 1	Placebo	Pimavanserin 20 mg	Pimavanserin 34 mg
Started	40	35	36
Completed	27	27	29
Not completed	13	8	7
Consent withdrawn by subject	-	2	1
Physician decision	-	-	1
Adverse event, non-fatal	4	1	3
Non-compliance with study drug	2	-	-
Caregiver withdrew consent	2	3	2
Progressive disease	1	-	-
Lack of efficacy	2	-	-
Protocol deviation	2	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo, taken as two tablets, once daily by mouth	
Reporting group title	Pimavanserin 20 mg
Reporting group description:	
Drug- pimavanserin tartrate, 20 mg, taken as two 10 mg tablets, once daily by mouth	
Reporting group title	Pimavanserin 34 mg
Reporting group description:	
Drug- pimavanserin tartrate, 34 mg, taken as two 17 mg tablets, once daily by mouth	

Reporting group values	Placebo	Pimavanserin 20 mg	Pimavanserin 34 mg
Number of subjects	40	35	36
Age categorical Units: Subjects			
Adults (18-64 years)	2	4	3
From 65-84 years	29	23	28
85 years and over	9	8	5
Age continuous Units: years			
arithmetic mean	78.9	76.5	75.0
standard deviation	± 7.58	± 8.74	± 7.90
Gender categorical Units: Subjects			
Female	25	15	18
Male	15	20	18

Reporting group values	Total		
Number of subjects	111		
Age categorical Units: Subjects			
Adults (18-64 years)	9		
From 65-84 years	80		
85 years and over	22		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	58		
Male	53		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo, taken as two tablets, once daily by mouth	
Reporting group title	Pimavanserin 20 mg
Reporting group description:	
Drug- pimavanserin tartrate, 20 mg, taken as two 10 mg tablets, once daily by mouth	
Reporting group title	Pimavanserin 34 mg
Reporting group description:	
Drug- pimavanserin tartrate, 34 mg, taken as two 17 mg tablets, once daily by mouth	

Primary: Cohen-Mansfield Agitation Inventory (CMAI)

End point title	Cohen-Mansfield Agitation Inventory (CMAI)
End point description:	
Change from Baseline to Week 12 in the Cohen-Mansfield Agitation Inventory (CMAI) total score. The CMAI is a 29-item scale designed to systematically assess agitation, rated on a 7-point (1-7) scale of frequency. Higher scores indicate worse outcome.	
End point type	Primary
End point timeframe:	
Approximately 12 weeks	

End point values	Placebo	Pimavanserin 20 mg	Pimavanserin 34 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37[1]	34[2]	35[3]	
Units: Score points				
arithmetic mean (standard error)				
Baseline	70.3 (± 4.5)	56.9 (± 2.2)	68.0 (± 3.3)	
Week 12	54.3 (± 4.3)	52.5 (± 4.3)	53.7 (± 3.0)	
Week 12 change from baseline	-16.8 (± 5.0)	-3.7 (± 3.7)	-12.3 (± 2.7)	

Notes:

[1] - Patients randomised and treated and with both a baseline and at least 1 post-baseline CMAI score

[2] - Patients randomised and treated and with both a baseline and at least 1 post-baseline CMAI score

[3] - Patients randomised and treated and with both a baseline and at least 1 post-baseline CMAI score

Statistical analyses

Statistical analysis title	Primary endpoint, pimavanserin 20 mg vs placebo
Statistical analysis description:	
Mixed-effect model repeated measures (MMRM), with the dependent variable being the change from Baseline in CMAI total score.	
Comparison groups	Placebo v Pimavanserin 20 mg

Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Difference in LSM
Point estimate	5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	15
Variability estimate	Standard error of the mean
Dispersion value	5

Statistical analysis title	Primary endpoint, pimavanserin 34 mg vs placebo

Statistical analysis description:

Mixed-effect model repeated measures (MMRM), with the dependent variable being the change from Baseline in CMAI total score.

Comparison groups	Placebo v Pimavanserin 34 mg
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Difference in LSM
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	10.5
Variability estimate	Standard error of the mean
Dispersion value	4.8

Secondary: Zarit Burden Interview

End point title	Zarit Burden Interview

End point description:

The ZBI was designed to assess the stresses experienced by caregivers of patients with dementia. It comprises a series of 22 questions about the impact of the patient’s disabilities on their life. For each item, caregivers are to indicate how often they felt that way (never, rarely, sometimes, quite frequently, or nearly always). Higher scores indicate worse outcome.

End point type	Secondary

End point timeframe:

Approximately 12 weeks

End point values	Placebo	Pimavanserin 20 mg	Pimavanserin 34 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34[4]	33[5]	32[6]	
Units: Score points				
arithmetic mean (standard error)				
Baseline	41.5 (± 2.6)	40.8 (± 2.4)	41.7 (± 2.5)	
Week 12	37.0 (± 3.2)	36.8 (± 3.7)	35.7 (± 3.5)	
Week 12 change from baseline	-6.5 (± 2.3)	-4.9 (± 2.3)	-5.5 (± 2.5)	

Notes:

[4] - Patients randomised and treated and with both a baseline and at least 1 post-baseline CMAI score

[5] - Patients randomised and treated and with both a baseline and at least 1 post-baseline CMAI score

[6] - Patients randomised and treated and with both a baseline and at least 1 post-baseline CMAI score

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of informed consent through the completion of procedures at the Week 12 visit (for subjects continuing into an Open-Label Extension study) or through to 30 days after the last dose of study drug (for all other subjects)

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	Placebo

Reporting group description:

Placebo, taken as two tablets, once daily by mouth

Reporting group title	Pimavanserin 20 mg

Reporting group description:

Drug- pimavanserin tartrate, 20 mg, taken as two 10 mg tablets, once daily by mouth

Reporting group title	Pimavanserin 34 mg

Reporting group description:

Drug- pimavanserin tartrate, 34 mg, taken as two 17 mg tablets, once daily by mouth

Serious adverse events	Placebo	Pimavanserin 20 mg	Pimavanserin 34 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 40 (7.50%)	4 / 35 (11.43%)	3 / 36 (8.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Weight decreased			
subjects affected / exposed	1 / 40 (2.50%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 40 (0.00%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			

subjects affected / exposed	0 / 40 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 40 (0.00%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diverticulum			
subjects affected / exposed	0 / 40 (0.00%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 40 (0.00%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 40 (2.50%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 40 (2.50%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 40 (0.00%)	1 / 35 (2.86%)	2 / 36 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			

subjects affected / exposed	0 / 40 (0.00%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Pimavanserin 20 mg	Pimavanserin 34 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 40 (27.50%)	15 / 35 (42.86%)	15 / 36 (41.67%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 40 (2.50%)	1 / 35 (2.86%)	2 / 36 (5.56%)
occurrences (all)	1	2	2
Fall			
subjects affected / exposed	1 / 40 (2.50%)	3 / 35 (8.57%)	3 / 36 (8.33%)
occurrences (all)	1	3	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 40 (2.50%)	2 / 35 (5.71%)	0 / 36 (0.00%)
occurrences (all)	1	2	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 40 (2.50%)	2 / 35 (5.71%)	2 / 36 (5.56%)
occurrences (all)	1	2	2
Diarrhoea			
subjects affected / exposed	3 / 40 (7.50%)	2 / 35 (5.71%)	2 / 36 (5.56%)
occurrences (all)	3	2	2
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 40 (0.00%)	2 / 35 (5.71%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			

Agitation			
subjects affected / exposed	5 / 40 (12.50%)	5 / 35 (14.29%)	1 / 36 (2.78%)
occurrences (all)	5	5	1
Insomnia			
subjects affected / exposed	0 / 40 (0.00%)	4 / 35 (11.43%)	3 / 36 (8.33%)
occurrences (all)	0	5	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 35 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2
Urinary tract infection			
subjects affected / exposed	0 / 40 (0.00%)	2 / 35 (5.71%)	1 / 36 (2.78%)
occurrences (all)	0	2	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 40 (0.00%)	2 / 35 (5.71%)	2 / 36 (5.56%)
occurrences (all)	0	2	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2016	- Primary efficacy endpoint changed from NPI-C to CMAI total score - Key secondary efficacy endpoint changed from NPI total caregiver distress score to ZBI total score - Changed secondary objective for efficacy evaluation of pimavanserin vs placebo for cognition to exploratory objective - Revised secondary efficacy endpoints assessment scale from NPI to NPI-C; specified timeframes for evaluation
18 July 2017	- Changed IN 1 (clarify requirement for informed consent (IC) if subject not competent to provide IC) - Changed IN 8 (clarify eligibility of subjects capable to visit clinic as outpatient) - Added suicidal ideation and behavior as safety assessment
20 November 2017	The original planned sample size was approximately 432. For business reasons, and not related to safety, enrollment (randomisation) of new subjects into the study was stopped after 111 subjects were randomised. The Amendment: - Revised study objectives, number of planned subjects, description of endpoints, exploratory objectives and endpoints, statistical methods - Specified that this study was not powered to detect differences between the Treatment groups due to early termination by the Sponsor and consequent reduced sample size - Revised PK endpoints and specified that only the plasma concentration data would be provided; this change was made to align with the study termination and resultant limited number of subjects that would not support additional analyses - For all efficacy endpoints, removed hypothesis testing and sensitivity analyses and specified that only descriptive summaries would be provided for evaluation of efficacy; this change was made to align with the study termination

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.

The original study (n=432) was powered to detect a treatment effect on CMAI however recruitment was discontinued early for business reasons and amended accordingly The final study (n=111) was no longer adequately powered to detect a treatment effect

Notes: