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

Summary

EudraCT number	2010-020008-31
Trial protocol	GB
Global end of trial date	27 October 2016

Results information

Result version number	v1 (current)
This version publication date	11 November 2017
First version publication date	11 November 2017

Trial information

Trial identification

Sponsor protocol code	ACP-103-019

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02035553
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	James Youakim, Vice President, Clinical Development & Clinical Research, ACADIA Pharmaceuticals Inc., +1 609-250-6900, jyouakim@acadia-pharm.com
Scientific contact	James Youakim, Vice President, Clinical Development & Clinical Research, ACADIA Pharmaceuticals Inc., +1 609-250-6900, jyouakim@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	27 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 October 2016
Global end of trial reached?	Yes
Global end of trial date	27 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of pimavanserin in subjects with Alzheimer’s disease psychosis (ADP) after 6 weeks of treatment

Protection of trial subjects:

A Data Monitoring Ethics Committee (DMEC) reviewed the safety and clinical outcome data of subjects at regular intervals

Background therapy:

None

Evidence for comparator: -

Actual start date of recruitment	16 January 2014
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	United Kingdom: 181
Worldwide total number of subjects	181
EEA total number of subjects	181

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)	1
From 65 to 84 years	69
85 years and over	111

Subject disposition

Recruitment

Recruitment details:

The study was performed in subjects with Alzheimer's Disease (AD) who were to have had at least a one-month history of psychotic symptoms that developed after the diagnosis of AD was established, and active psychotic symptoms in the month prior to the Screening Visit. A total of 345 unique subjects were screened.

Pre-assignment

Screening details:

Prior to randomisation, subjects entered a 3-week screening period with antipsychotic medication washout. During this period, subjects received brief psychosocial therapy following best practice guidelines, and safety assessments were performed.

Period 1

Period 1 title	Treatment period (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, 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:

Two placebo tablets, once daily by mouth, during the treatment period (Week 1 to 12)

Arm title	Pimavanserin tartrate 40 mg (equivalent to 34 mg pimavanserin)

Arm description:

Pimavanserin tartrate 40 mg (two 20 mg tablets), once daily by mouth (equivalent to 34 mg pimavanserin)

Arm type	Experimental
Investigational medicinal product name	Pimavanserin
Investigational medicinal product code	ACP-103
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Plimavanserin tartrate 40 mg (two 20 mg tablets), equivalent to 34 mg pimavanserin (two 17 mg tablets), taken once daily by mouth during the treatment period (Week 1 to 12)

Number of subjects in period 1	Placebo	Pimavanserin tartrate 40 mg (equivalent to 34 mg pimavanserin)
Started	91	90
Completed	73	67
Not completed	18	23
Physician decision	3	2
Consent withdrawn by subject	4	7
Adverse event, non-fatal	10	6
Other	-	4
Death (see Serious Adverse Event Table)	-	1
Non-compliance with study drug	-	1
Lost to follow-up	-	1
Lack of efficacy	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo, two tablets, once daily by mouth	
Reporting group title	Pimavanserin tartrate 40 mg (equivalent to 34 mg pimavanserin)
Reporting group description:	
Pimavanserin tartrate 40 mg (two 20 mg tablets), once daily by mouth (equivalent to 34 mg pimavanserin)	

Reporting group values	Placebo	Pimavanserin tartrate 40 mg (equivalent to 34 mg pimavanserin)	Total
Number of subjects	91	90	181
Age categorical 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)	0	0	0
Adults (18-64 years)	1	0	1
From 65-84 years	32	37	69
85 years and over	58	53	111
Age continuous Units: years			
arithmetic mean	86.1	85.7	
standard deviation	± 5.96	± 7.05	-
Gender categorical Units: Subjects			
Female	73	73	146
Male	18	17	35
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	91	90	181
Unknown or Not Reported	0	0	0
Race Units: Subjects			
Asian	0	3	3
Black or African American	1	3	4
White	89	84	173
Other	1	0	1

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo, two tablets, once daily by mouth	
Reporting group title	Pimavanserin tartrate 40 mg (equivalent to 34 mg pimavanserin)
Reporting group description: Pimavanserin tartrate 40 mg (two 20 mg tablets), once daily by mouth (equivalent to 34 mg pimavanserin)	

Primary: Change from baseline to Day 43 in the NPI-NH psychosis score (Delusions [Domain A]+Hallucinations [Domain B])

End point title	Change from baseline to Day 43 in the NPI-NH psychosis score (Delusions [Domain A]+Hallucinations [Domain B])

End point description:

Change from Baseline to Day 43 in the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH) psychosis score (Delusions [Domain A]+Hallucinations [Domain B]) in the Full Analysis Set. The NPI-NH is a questionnaire that quantifies behavioral changes in dementia in nursing home patients and evaluates 12 behavioral domains. For each of the 12 behavioral domains the Frequency (scale:1=occasionally to 4=very frequently) is multiplied by the Severity (scale:1=Mild to 3=Severe) to obtain a domain score (frequency x severity). The NPI-NH psychosis score consists of the 2 domains of Delusions and Hallucinations, calculated by adding the Individual domain scores, to yield a possible total score of 0 to 24. Lower scores correspond to less severity. A negative change score from baseline indicates improvement.

End point type	Primary

End point timeframe:

Day 43

End point values	Placebo	Pimavanserin tartrate 40 mg (equivalent to 34 mg pimavanserin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91[1]	87[2]		
Units: Score				
least squares mean (confidence interval 95%)	-1.93 (-3.18 to -0.67)	-3.76 (-5.05 to -2.47)		

Notes:

[1] - Randomised subjects with >=1 dose of Treatment and baseline and >=1 post-baseline assessment

[2] - Randomised subjects with >=1 dose of Treatment and baseline and >=1 post-baseline assessment

Statistical analyses

Statistical analysis title	Primary endpoint

Statistical analysis description:

The primary efficacy endpoint was the mean change from Baseline to Day 43 in the NPI-NH psychosis score (delusions + hallucinations), analysed using a mixed-effects model for repeated measurements (MMRM).

Comparison groups	Placebo v Pimavanserin tartrate 40 mg (equivalent to 34 mg pimavanserin)
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0451
Method	Mixed models analysis
Parameter estimate	Difference in MMRM LSM
Point estimate	-1.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.64
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.91

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 weeks

Adverse event reporting additional description:

From the time of signing informed consent, adverse events were to be reported through the 12-week treatment period and up to the follow-up phone call that was performed 4 weeks after the end of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo, two tablets, once daily by mouth

Reporting group title	Pimavanserin tartrate 40 mg (equivalent to 34 mg pimavanserin)

Reporting group description:

Pimavanserin tartrate 40 mg (two 20 mg tablets), once daily by mouth (equivalent to 34 mg pimavanserin)

Serious adverse events	Placebo	Pimavanserin tartrate 40 mg (equivalent to 34 mg pimavanserin)	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 91 (10.99%)	15 / 90 (16.67%)	
number of deaths (all causes)	4	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm of thorax			
subjects affected / exposed	0 / 91 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 91 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			

subjects affected / exposed	0 / 91 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 91 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 91 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 91 (1.10%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 91 (1.10%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 91 (1.10%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 91 (1.10%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	1 / 91 (1.10%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			

subjects affected / exposed	2 / 91 (2.20%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dementia			
subjects affected / exposed	0 / 91 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Depressed level of consciousness			
subjects affected / exposed	0 / 91 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 91 (1.10%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 91 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 91 (1.10%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 91 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			

subjects affected / exposed	0 / 91 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 91 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lower respiratory tract infection			
subjects affected / exposed	0 / 91 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 91 (2.20%)	2 / 90 (2.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 1	
Urinary tract infection			
subjects affected / exposed	0 / 91 (0.00%)	2 / 90 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Pimavanserin tartrate 40 mg (equivalent to 34 mg pimavanserin)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 91 (76.92%)	67 / 90 (74.44%)	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	8 / 91 (8.79%)	3 / 90 (3.33%)	
occurrences (all)	8	3	
Blood lactate dehydrogenase increased			
subjects affected / exposed	10 / 91 (10.99%)	4 / 90 (4.44%)	
occurrences (all)	10	4	

Blood potassium increased			
subjects affected / exposed	3 / 91 (3.30%)	5 / 90 (5.56%)	
occurrences (all)	3	5	
Blood urea increased			
subjects affected / exposed	8 / 91 (8.79%)	7 / 90 (7.78%)	
occurrences (all)	8	7	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	14 / 91 (15.38%)	11 / 90 (12.22%)	
occurrences (all)	17	16	
Fall			
subjects affected / exposed	21 / 91 (23.08%)	20 / 90 (22.22%)	
occurrences (all)	35	39	
Laceration			
subjects affected / exposed	5 / 91 (5.49%)	3 / 90 (3.33%)	
occurrences (all)	6	3	
Nervous system disorders			
Somnolence			
subjects affected / exposed	7 / 91 (7.69%)	3 / 90 (3.33%)	
occurrences (all)	7	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 91 (8.79%)	9 / 90 (10.00%)	
occurrences (all)	8	9	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	2 / 91 (2.20%)	7 / 90 (7.78%)	
occurrences (all)	2	7	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	7 / 91 (7.69%)	4 / 90 (4.44%)	
occurrences (all)	7	4	
Psychiatric disorders			
Aggression			
subjects affected / exposed	4 / 91 (4.40%)	9 / 90 (10.00%)	
occurrences (all)	4	10	
Agitation			

subjects affected / exposed	13 / 91 (14.29%)	19 / 90 (21.11%)	
occurrences (all)	13	19	
Anxiety			
subjects affected / exposed	2 / 91 (2.20%)	5 / 90 (5.56%)	
occurrences (all)	2	5	
Behavioural and psychiatric symptoms of dementia			
subjects affected / exposed	2 / 91 (2.20%)	5 / 90 (5.56%)	
occurrences (all)	2	6	
Infections and infestations			
Cellulitis			
subjects affected / exposed	3 / 91 (3.30%)	6 / 90 (6.67%)	
occurrences (all)	3	7	
Lower respiratory tract infection			
subjects affected / exposed	12 / 91 (13.19%)	13 / 90 (14.44%)	
occurrences (all)	13	15	
Urinary tract infection			
subjects affected / exposed	25 / 91 (27.47%)	18 / 90 (20.00%)	
occurrences (all)	36	27	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	11 / 91 (12.09%)	4 / 90 (4.44%)	
occurrences (all)	11	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 July 2013	Key amendment changes: -Study design was changed from multi-centre to single-centre -Consent process clarifications made for staff/caregivers -Entry criteria were revised to clarify symptoms of ADP and broaden allowed MMSE score range -Modifications to clinical laboratory and ECG test schedule and/or methods -Sample size assumptions adjusted and statistical analysis methods were modified -Stratification criteria added for cognition and severity of psychosis -DMEC included in study
24 January 2014	Key amendment changes: -Various procedural clarifications -Modifications to several rating instruments were made to enhance the practical application of the assessments -The analysis plan was updated to accommodate the stratified study design and to specify evaluation of cognition
16 November 2015	Key amendment changes: -The description of the primary efficacy endpoint updated to change from baseline to D43 for NPI-NH psychosis score (Delusions + Hallucinations domains A and B); and other efficacy endpoints were revised and/or categorized as being either secondary or exploratory. -Various procedural clarifications -Clarifications to exclusion criteria and prohibited and concomitant medications

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported