Clinical trial results:
A Double-blind, Placebo-controlled, Relapse Prevention Study of Pimavanserin for the Treatment of Hallucinations and Delusions Associated With Dementia-related Psychosis

Summary

EudraCT number	2017-002227-13
Trial protocol	GB CZ SK BG ES PL FR IT
Global end of trial date	30 October 2019

Results information

Result version number	v1 (current)
This version publication date	16 May 2021
First version publication date	16 May 2021

Trial information

Trial identification

Sponsor protocol code	ACP-103-045

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03325556
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 2612897, medicalinformation@acadia-pharm.com
Scientific contact	Sr. Dir. Medical Information and Medical Communications, Acadia Pharmaceuticals Inc., +1 858 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	31 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2019
Global end of trial reached?	Yes
Global end of trial date	30 October 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate relapse prevention in subjects with dementia-related psychosis treated with pimavanserin compared to placebo

Protection of trial subjects:

Not applicable

Background therapy:

No

Evidence for comparator:

-

Actual start date of recruitment	31 August 2017
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	Poland: 42
Country: Number of subjects enrolled	Slovakia: 35
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Czechia: 11
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	United States: 118
Country: Number of subjects enrolled	Ukraine: 74
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	Chile: 27
Country: Number of subjects enrolled	Serbia: 44
Worldwide total number of subjects	392
EEA total number of subjects	129

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)	54
From 65 to 84 years	299
85 years and over	39

Subject disposition

Recruitment

Recruitment details:

The study was performed in subjects with all-cause dementia according to NIA-AA guidelines, including dementia associated with Parkinson's disease, dementia with Lewy Bodies, possible/probable Alzheimer's disease, frontotemporal degeneration spectrum disorder, or vascular dementia, and were to have had >=2-month history of psychotic symptoms.

Pre-assignment

Screening details:

During the screening period, subjects were assessed for study eligibility and prohibited medications were discontinued when medically appropriate. Subjects and partner/caregivers also received a standardized psychosocial therapy training.

Period 1

Period 1 title	Open-Label Period
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Pimavanserin OL period

Arm description:

Pimavanserin 34 mg once daily, with the possibility to adjust to pimavanserin 20 mg once daily between Weeks 1 and 4 based on tolerability. After Week 4, the dose of study drug remained fixed at either 34 or 20 mg 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 once daily with the possibility to adjust to pimavanserin 20 mg once daily between Weeks 1 and 4 based on tolerability. After Week 4, the dose of study drug remained fixed at either 34 or 20 mg once daily.

Number of subjects in period 1	Pimavanserin OL period
Started	392
Completed	217
Not completed	175
Adverse event, serious fatal	1
Consent withdrawn by subject	17
Lack of response in OL period	70
Adverse event, non-fatal	27
Not otherwise specified	8

Noncompliance with study drug	5
Administrative discont. at study termination	41
Use of prohibited medication	1
Lost to follow-up	1
Protocol deviation	4

Period 2

Period 2 title	Double-blind period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Pimavanserin DB Period

Arm description:

Pimavanserin 34 mg once daily or pimavanserin 20 mg once daily (the dose at which patients completed the Open-Label Period) for 26 weeks or until relapse

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 once daily or pimavanserin 20 mg once daily (the dose at which patients completed the Open-Label Period) for 26 weeks or until relapse

Arm title	Placebo DB Period

Arm description:

Placebo once daily for 26 weeks or until relapse

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 once daily for 26 weeks or until relapse

Number of subjects in period 2	Pimavanserin DB Period	Placebo DB Period
Started	105	112
Completed	44	35
Not completed	61	77
Relapse	15	34
Consent withdrawn by subject	6	4
Physician decision	-	1
Adverse event, non-fatal	3	1
Not otherwise specified	1	5
Noncompliance with study drug	-	1
Administrative discont. at study termination	35	31
Use of prohibited medication	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Open-Label Period

Reporting group description:

Pimavanserin 34 mg once daily, with the possibility to adjust to pimavanserin 20 mg once daily between Weeks 1 and 4 based on tolerability. After Week 4, the dose of study drug remained fixed at either 34 or 20 mg once daily.

Reporting group values	Open-Label Period	Total	
Number of subjects	392	392	
Age categorical Units: Subjects			
Adults (18-64 years)	54	54	
From 65-84 years	299	299	
85 years and over	39	39	
Age continuous Units: years			
arithmetic mean	74.5		
standard deviation	± 8.28	-	
Gender categorical Units: Subjects			
Female	229	229	
Male	163	163	
Dementia severity Units: Subjects			
Mild	65	65	
Moderate	275	275	
Severe	52	52	
SAPS-H+D total score			
SAPS-H+D (Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions) is a 20-item scale; the total score is the sum of the 20 item scores (range 0-100); higher scores denote more severe Symptoms.			
Units: score on a scale			
arithmetic mean	24.4		
standard deviation	± 9.22	-	
Clinical Global Impression Severity (CGI-S) Units: units on a scale			
arithmetic mean	4.7		
standard deviation	± 0.69	-	

End points

End points reporting groups

Reporting group title	Pimavanserin OL period

Reporting group description:

Pimavanserin 34 mg once daily, with the possibility to adjust to pimavanserin 20 mg once daily between Weeks 1 and 4 based on tolerability. After Week 4, the dose of study drug remained fixed at either 34 or 20 mg once daily.

Reporting group title	Pimavanserin DB Period

Reporting group description:

Pimavanserin 34 mg once daily or pimavanserin 20 mg once daily (the dose at which patients completed the Open-Label Period) for 26 weeks or until relapse

Reporting group title	Placebo DB Period

Reporting group description:

Placebo once daily for 26 weeks or until relapse

Primary: Time From Randomization to Relapse in the Double-blind (DB) Period

End point title	Time From Randomization to Relapse in the Double-blind (DB) Period

End point description:

Time from randomization to relapse in the DB period was compared between treatment groups using a Cox regression model. The treatment effect was measured by the hazard ratio (HR).
Relapse was defined as (1) ≥30% increase in SAPS-H+D total score from DB baseline (BL) and CGI-I score ≥6 relative to DB BL, (2) treatment with antipsychotic for dementia-related delusions/hallucinations, (3) treatment/study discontinuation due to lack of efficacy, and/or (4) hospitalisation for worsening dementia-related psychosis.
CGI-I is a clinician-rated 7-point scale to rate improvement in hallucinations/delusions relative to BL (range 1-7); higher scores denote less improvement or worsening.
A pre-specified IA was conducted after 40 adjudicated relapse events had accrued during the study. The prespecified stopping criterion was met; the study was stopped for efficacy. The median time to relapse could not be estimated as the KM estimate of relapse over the 26-week DB period did not exceed 50%.

End point type	Primary

End point timeframe:

From randomization in the DB period through 26 weeks

End point values	Pimavanserin DB Period	Placebo DB Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95[1]	99[2]		
Units: Patients				
Patients relapsing	12	28		

Notes:

[1] - All patients randomized on or before the database cutoff date for the IA.

[2] - All patients randomized on or before the database cutoff date for the IA.

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

Time from randomization to relapse in the DB period was compared between treatment groups using a

Cox regression model. The treatment effect was measured by HR.
The median time to relapse could not be estimated as the Kaplan-Meier probability estimate of relapse over the 26-week DB period did not exceed 50%.

Comparison groups	Pimavanserin DB Period v Placebo DB Period
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0023 [4]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.353
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.172
upper limit	0.727
Variability estimate	Standard error of the mean
Dispersion value	0.3676

Notes:

[3] - Cox regression model included covariates for Treatment group, designated Dementia subtype, and region, and robust sandwich-type variance estimator.
[4] - 1-sided p-value reported. The protocol-defined O'Brien Flemming stopping boundary for the planned IA was a 1-sided p-value equal to 0.0033.

Secondary: Time From Randomization to Discontinuation From the DB Period for Any Reason

End point title	Time From Randomization to Discontinuation From the DB Period for Any Reason

End point description:

The endpoint of time from randomization to discontinuation from the DB period for any reason (other than termination of the study by the sponsor) was compared between treatment groups using a Cox regression model. The treatment effect was measured by the HR.
The median time to discontinuation could not be estimated as the Kaplan-Meier probability estimate of discontinuation over the 26-week DB period did not exceed 50%.

End point type	Secondary

End point timeframe:

From randomization in the DB period through 26 weeks

End point values	Pimavanserin DB Period	Placebo DB Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95[5]	99[6]		
Units: Patients				
Patients who discontinued	21	38		

Notes:

[5] - All patients randomized on or before the database cutoff date for the IA.

[6] - All patients randomized on or before the database cutoff date for the IA.

Statistical analyses

Statistical analysis title	Secondary analysis

Statistical analysis description:

Time from randomization to discontinuation in the DB period was compared between treatment groups

using a Cox regression model. The treatment effect was measured by HR.
The median time to discontinuation could not be estimated as the Kaplan-Meier probability estimate of discontinuation over the 26-week DB period did not exceed 50%.

Comparison groups	Pimavanserin DB Period v Placebo DB Period
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.0024 [8]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.452
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.261
upper limit	0.785
Variability estimate	Standard error of the mean
Dispersion value	0.2812

Notes:

[7] - Cox regression model included covariates for Treatment group, designated Dementia subtype, and region, and robust sandwich-type variance estimator.
[8] - 1-sided p-value reported

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	22.0

Reporting groups

Reporting group title	Pimavanserin OL period

Reporting group description:

Pimavanserin 34 mg once daily, with the possibility to adjust to pimavanserin 20 mg once daily between Weeks 1 and 4 based on tolerability. After Week 4, the dose of study drug remained fixed at either 34 or 20 mg once daily.

Reporting group title	Pimavanserin DB period

Reporting group description:

Pimavanserin 34 mg once daily or pimavanserin 20 mg once daily (the dose at which patients completed the Open-Label Period) for 26 weeks or until relapse.

Reporting group title	Placebo DB period

Reporting group description:

Placebo once daily for 26 weeks or until relapse

Serious adverse events	Pimavanserin OL period	Pimavanserin DB period	Placebo DB period
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 392 (5.10%)	5 / 105 (4.76%)	4 / 112 (3.57%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer metastatic			
subjects affected / exposed	0 / 392 (0.00%)	1 / 105 (0.95%)	0 / 112 (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
Injury, poisoning and procedural complications			
Bone fissure			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (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
Fall			

subjects affected / exposed	2 / 392 (0.51%)	0 / 105 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (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
Myocardial infarction			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Dementia Alzheimer's type			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (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
Metabolic encephalopathy			
subjects affected / exposed	0 / 392 (0.00%)	1 / 105 (0.95%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Syncope			
subjects affected / exposed	0 / 392 (0.00%)	0 / 105 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 392 (0.00%)	1 / 105 (0.95%)	0 / 112 (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
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (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

Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (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
Abdominal pain upper			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (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
Diarrhoea			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (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
Haematemesis			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (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	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (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
Agression			
subjects affected / exposed	1 / 392 (0.26%)	1 / 105 (0.95%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (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

Neuropsychiatric symptoms			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (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
Infections and infestations			
Abscess jaw			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (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
Diverticulitis			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (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
Erysipelas			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (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
Pneumonia			

subjects affected / exposed	0 / 392 (0.00%)	0 / 105 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 392 (0.00%)	1 / 105 (0.95%)	0 / 112 (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
Septic encephalopathy			
subjects affected / exposed	0 / 392 (0.00%)	1 / 105 (0.95%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 392 (0.51%)	1 / 105 (0.95%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 392 (0.00%)	0 / 105 (0.00%)	1 / 112 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	2 / 392 (0.51%)	0 / 105 (0.00%)	0 / 112 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	1 / 392 (0.26%)	0 / 105 (0.00%)	0 / 112 (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

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

Non-serious adverse events	Pimavanserin OL period	Pimavanserin DB period	Placebo DB period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 392 (6.12%)	16 / 105 (15.24%)	9 / 112 (8.04%)
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 392 (1.53%)	10 / 105 (9.52%)	5 / 112 (4.46%)
occurrences (all)	6	13	8
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	18 / 392 (4.59%)	6 / 105 (5.71%)	4 / 112 (3.57%)
occurrences (all)	19	8	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2018	Clarifications of the following items were introduced: - IN criteria (clarified definition of stable use of Cholinesterase inhibitors/memantine; acceptable methods of birth control) - EX criteria (provision of NYHA Grading Scale; ECG parameters for pts on certain antidepressants; Parameters required to allow repeat HR; exclusion of pts with severe renal or hepatic impairment; criteria for repeat laboratory testing; clarifications on intracranial aneurysm exclusions; urine drug screening process) - Clarifying study discontinuation and completion definitions - Extension of Screening period to allow for confirmatory testing - Sample size calculation; methodology for determining statistical significance at interim and final analyses - Subject discontinuation procedures - Allowance of a brain MRI with contrast or a head CT with contrast if clinically warranted - Laboratory Evaluations - Included a maximum number of randomized pts in the study (n=400) - Procedures clarified for prohibited medication - Laboratory testing at screening (magnesium; TSH and free T4) - Added temperature as a vital sign measurement

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
31 July 2019	A protocol-specified interim analysis (IA) was performed after 40 relapse events had been adjudicated by an independent adjudication committee (IAC). The study was terminated following positive IA results, which met the prespecified stopping criteria for efficacy.	-

Notes:

Limitations and caveats

None reported