



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 discount 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 | Subject, Investigator, Monitor, Data analyst, Carer, 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 discontin. 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) $\geq 30\%$ 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 Fleming 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 occurrences (all) | 6 / 392 (1.53%) 6 | 10 / 105 (9.52%) 13 | 5 / 112 (4.46%) 8 |
| Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) | 18 / 392 (4.59%) 19 | 6 / 105 (5.71%) 8 | 4 / 112 (3.57%) 5 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|--|
| 16 August 2018 | <p>Clarifications of the following items were introduced:</p> <ul style="list-style-type: none">- 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