



## Clinical trial results:

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

#### Summary

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

#### Results information

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

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | ACP-103-033 |
|-----------------------|-------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | ACADIA Pharmaceuticals Inc.  |
| Sponsor organisation address | 3611 Valley Centre Drive, Ste. 300, San Diego, CA, United States, 92130  |
| Public contact               | Sr. Dir. Medical Information and Medical Communications, ACADIA Pharmaceuticals Inc., +1 858-261-2897, medicalinformation@acadia-pharm.com |
| Scientific contact           | Sr. Dir. Medical Information and Medical Communications, ACADIA Pharmaceuticals Inc., +1 858-261-2897, medicalinformation@acadia-pharm.com |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 25 February 2019 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 25 February 2019 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 25 February 2019 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

Not applicable

Background therapy:

No specific background therapy was specified.

Patients were to continue any concomitant antidepressants, cholinesterase inhibitors, memantine, and other permitted medications at stable doses throughout the study.

Evidence for comparator:

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

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 22 February 2017 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Spain: 6          |
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Country: Number of subjects enrolled | France: 6         |
| Country: Number of subjects enrolled | Chile: 29         |
| Country: Number of subjects enrolled | United States: 33 |
| Worldwide total number of subjects   | 78                |
| EEA total number of subjects         | 16                |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |
| Children (2-11 years)                     | 0 |

|                           |    |
|---------------------------|----|
| Adolescents (12-17 years) | 0  |
| Adults (18-64 years)      | 5  |
| From 65 to 84 years       | 58 |
| 85 years and over         | 15 |

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

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

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

Blinding implementation details:

Not applicable

### Arms

|           |              |
|-----------|--------------|
| Arm title | All patients |
|-----------|--------------|

Arm description:

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

Subsequently, the dose could be adjusted from 34 mg to 20 mg or from 20 mg to 34 mg at any visit based on clinical response.

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

Dosage and administration details:

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

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

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

## Baseline characteristics

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | All patients |
|-----------------------|--------------|

Reporting group description:

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

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

## End points

### End points reporting groups

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

### Primary: Treatment-emergent adverse events (TEAEs)

|  |  |
|--|--|
| End point title  | Treatment-emergent adverse events (TEAEs) <sup>[1]</sup> |
| End point description:   |  |
| Safety and tolerability of pimavanserin after 52 weeks of treatment in patients with probable Alzheimer's disease who have symptoms of agitation and Aggression, in terms of occurrence of TEAEs |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| 52 weeks   |  |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

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

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

52 weeks

Adverse event reporting additional description:

Not applicable

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | All patients |
|-----------------------|--------------|

Reporting group description:

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

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



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

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

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 18 July 2017     | <ul style="list-style-type: none"><li>- Added exclusion criteria for patients receiving skilled nursing care for any medical condition other than dementia and for patients with a Global Clinician Assessment of Suicidality (GCAS) score of 3 or 4 based on Investigator's assessment of behavior since the last assessment.</li><li>- Added GCAS as a primary endpoint</li><li>- Specified that the Neuropsychiatric Inventory-Clinician rating scale (NPI-C) was rated by the clinician for patients not able to provide reliable information (e.g. due to cognitive impairment).</li><li>- Removed AEs of special interest</li><li>- Added suicidal ideation and behavior as additional safety assessment</li></ul> |
| 30 November 2017 | <p>The protocol of the parent study ACP-103-032 was amended on 20 Nov 2017 to stop enrollment of new patients for business reasons, not related to safety. Enrollment was stopped when 111 of approximately 432 planned patients had been randomised. Consequently, the planned patient number for this trial also had to be adjusted to 111.</p> <p>In addition, endpoint designations were changed i.e. TEAEs were made the primary endpoint; and previously defined secondary efficacy endpoints became exploratory endpoints.</p>  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported