



## Clinical trial results:

### A Phase 3, 182-week, Open-Label Extension Study to Investigate the Safety and Tolerability of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension (symptomatic nOH) in Subjects with Primary Autonomic Failure

#### Summary

|                          |                                     |
|--------------------------|-------------------------------------|
| EudraCT number           | 2019-002425-30                      |
| Trial protocol           | GB DK ES PL EE FR PT AT BG DE HU IT |
| Global end of trial date | 12 November 2021                    |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 15 December 2022 |
| First version publication date | 15 December 2022 |

#### Trial information

##### Trial identification

|                       |      |
|-----------------------|------|
| Sponsor protocol code | 0171 |
|-----------------------|------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04095793 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Theravance Biopharma Ireland Limited  |
| Sponsor organisation address | Ten Earlsfort Terrace, Dublin, Ireland, D02 T380                              |
| Public contact               | Richard Graham, Theravance Biopharma, +1 855 633 8479, medinfo@theravance.com |
| Scientific contact           | Richard Graham, Theravance Biopharma, +1 855 633 8479, medinfo@theravance.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                       | 12 November 2021 |
| Is this the analysis of the primary completion data? | No               |

|                                  |                  |
|----------------------------------|------------------|
| Global end of trial reached?     | Yes              |
| Global end of trial date         | 12 November 2021 |
| Was the trial ended prematurely? | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the long-term safety of TD-9855 over a 182-week period.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Harmonised Tripartite Guideline.

Background therapy: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 19 September 2019 |
| 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: 15            |
| Country: Number of subjects enrolled | Portugal: 2           |
| Country: Number of subjects enrolled | Spain: 6              |
| Country: Number of subjects enrolled | United Kingdom: 7     |
| Country: Number of subjects enrolled | Austria: 1            |
| Country: Number of subjects enrolled | Bulgaria: 3           |
| Country: Number of subjects enrolled | Denmark: 1            |
| Country: Number of subjects enrolled | Estonia: 1            |
| Country: Number of subjects enrolled | France: 2             |
| Country: Number of subjects enrolled | Germany: 7            |
| Country: Number of subjects enrolled | Italy: 9              |
| Country: Number of subjects enrolled | United States: 29     |
| Country: Number of subjects enrolled | Canada: 2             |
| Country: Number of subjects enrolled | Australia: 3          |
| Country: Number of subjects enrolled | Israel: 1             |
| Country: Number of subjects enrolled | New Zealand: 1        |
| Country: Number of subjects enrolled | Ukraine: 12           |
| Country: Number of subjects enrolled | Russian Federation: 8 |
| Worldwide total number of subjects   | 110                   |
| EEA total number of subjects         | 47                    |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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)                      | 31 |
| From 65 to 84 years                       | 78 |
| 85 years and over                         | 1  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 110 participants who completed Study 0170 rolled over into Study 0171. The study was performed in Europe, Asia/Pacific, and the United States between 19 September 2019 and 12 November 2021.

### Pre-assignment

Screening details:

The study was planned to consist of 3 periods: 26-week treatment, 156-week treatment extension, and 2-week follow-up.

### Period 1

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

### Arms

|           |             |
|-----------|-------------|
| Arm title | Amprexetine |
|-----------|-------------|

Arm description:

Participants received a single dose of 10 mg amprelosetine once daily (QD) for a planned duration of up to 182 weeks.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Amprexetine  |
| Investigational medicinal product code | TD-9855      |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Participants received 10 mg QD for a planned duration of up to 182 weeks.

| Number of subjects in period 1 | Amprexetine |
|--------------------------------|-------------|
| Started                        | 110         |
| Completed                      | 0           |
| Not completed                  | 110         |
| Consent withdrawn by subject   | 4           |
| Adverse event, non-fatal       | 3           |
| Study Terminated by Sponsor    | 103         |

## Baseline characteristics

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Amprexetine |
|-----------------------|-------------|

Reporting group description:

Participants received a single dose of 10 mg amprelosetine once daily (QD) for a planned duration of up to 182 weeks.

| Reporting group values                    | Amprexetine | Total |  |
|---|-------------|-------|--|
| Number of subjects                        | 110         | 110   |  |
| Age categorical                           |             |       |  |
| Units: Subjects                           |             |       |  |
| Age continuous                            |             |       |  |
| Units: years                              |             |       |  |
| arithmetic mean                           | 68.4        |       |  |
| standard deviation                        | ± 8.29      | -     |  |
| Gender categorical                        |             |       |  |
| Units: Subjects                           |             |       |  |
| Female                                    | 31          | 31    |  |
| Male                                      | 79          | 79    |  |
| Ethnicity                                 |             |       |  |
| Units: Subjects                           |             |       |  |
| Hispanic or Latino                        | 2           | 2     |  |
| Not Hispanic or Latino                    | 105         | 105   |  |
| Unknown or Not Reported                   | 3           | 3     |  |
| Race                                      |             |       |  |
| Units: Subjects                           |             |       |  |
| American Indian or Alaska Native          | 0           | 0     |  |
| Asian                                     | 1           | 1     |  |
| Native Hawaiian or Other Pacific Islander | 0           | 0     |  |
| Black or African American                 | 1           | 1     |  |
| White                                     | 108         | 108   |  |
| More than one race                        | 0           | 0     |  |
| Unknown or Not Reported                   | 0           | 0     |  |
| Primary Diagnosis                         |             |       |  |
| Units: Subjects                           |             |       |  |
| Multiple System Atrophy                   | 34          | 34    |  |
| Parkinson's Disease                       | 58          | 58    |  |
| Pure Autonomic Failure                    | 18          | 18    |  |

## End points

### End points reporting groups

|   |             |
|---|-------------|
| Reporting group title   | Amprexetine |
| Reporting group description:  |             |
| Participants received a single dose of 10 mg ampreloxetine once daily (QD) for a planned duration of up to 182 weeks. |             |

### Primary: Number of Participants With Treatment-emergent Adverse Events (TEAEs)

|                 |  |
|-----------------|--|
| End point title | Number of Participants With Treatment-emergent Adverse Events (TEAEs) <sup>[1]</sup> |
|-----------------|--|

End point description:

An adverse event (AE) was any untoward medical occurrence in a patient or clinical study participant administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. A TEAE was defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus the number of days in the follow-up period.

Clinically significant abnormalities in physical and neurological examinations, vital signs, resting 12-lead electrocardiograms, and clinical laboratory evaluations, in addition to incidence of fall, suicidal ideation, and suicidal behavior, were reported as AEs.

The safety set was defined as all enrolled participants who received at least 1 dose of ampreloxetine in the study.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 1 up to a maximum of 749 days

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: No additional statistical analysis was prespecified for this endpoint.

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Amprexetine     |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 110             |  |  |  |
| Units: participants         | 61              |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 1 up to a maximum of 749 days

Adverse event reporting additional description:

The safety set was defined as all enrolled participants who received at least 1 dose of ampreloxetine in the study.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Ampreloxetine |
|-----------------------|---------------|

Reporting group description:

Participants received a single dose of 10 mg ampreloxetine QD for a planned duration of up to 182 weeks.

| Serious adverse events                            | Ampreloxetine     |  |  |
|---|-------------------|--|--|
| Total subjects affected by serious adverse events |                   |  |  |
| subjects affected / exposed                       | 14 / 110 (12.73%) |  |  |
| number of deaths (all causes)                     | 1                 |  |  |
| number of deaths resulting from adverse events    | 1                 |  |  |
| Vascular disorders                                |                   |  |  |
| Orthostatic hypotension                           |                   |  |  |
| subjects affected / exposed                       | 1 / 110 (0.91%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 1             |  |  |
| deaths causally related to treatment / all        | 0 / 0             |  |  |
| Deep vein thrombosis                              |                   |  |  |
| subjects affected / exposed                       | 1 / 110 (0.91%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 1             |  |  |
| deaths causally related to treatment / all        | 0 / 0             |  |  |
| Cardiac disorders                                 |                   |  |  |
| Atrial fibrillation                               |                   |  |  |
| subjects affected / exposed                       | 1 / 110 (0.91%)   |  |  |
| occurrences causally related to treatment / all   | 1 / 1             |  |  |
| deaths causally related to treatment / all        | 0 / 0             |  |  |
| Nervous system disorders                          |                   |  |  |
| Loss of consciousness                             |                   |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                          | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Paraparesis  |                 |  |  |
| subjects affected / exposed                          | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Lethargy   |                 |  |  |
| subjects affected / exposed                          | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Sciatica   |                 |  |  |
| subjects affected / exposed                          | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Syncope  |                 |  |  |
| subjects affected / exposed                          | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Dizziness  |                 |  |  |
| subjects affected / exposed                          | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Chest pain   |                 |  |  |
| subjects affected / exposed                          | 2 / 110 (1.82%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Reproductive system and breast disorders             |                 |  |  |
| Prostatitis  |                 |  |  |
| subjects affected / exposed                          | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Pulmonary embolism                              |                 |  |  |
| subjects affected / exposed                     | 2 / 110 (1.82%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Decubitus ulcer                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Flank pain                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Cystitis  |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Urinary tract infection                         |                 |  |  |
| subjects affected / exposed                     | 2 / 110 (1.82%) |  |  |
| occurrences causally related to treatment / all | 0 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sepsis  |                 |  |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

Frequency threshold for reporting non-serious adverse events: 3 %

| <b>Non-serious adverse events</b>                     | Amprexetine       |  |  |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 24 / 110 (21.82%) |  |  |
| Nervous system disorders                              |                   |  |  |
| Headache  |                   |  |  |
| subjects affected / exposed                           | 6 / 110 (5.45%)   |  |  |
| occurrences (all)                                     | 8                 |  |  |
| General disorders and administration site conditions  |                   |  |  |
| Fatigue   |                   |  |  |
| subjects affected / exposed                           | 4 / 110 (3.64%)   |  |  |
| occurrences (all)                                     | 4                 |  |  |
| Reproductive system and breast disorders              |                   |  |  |
| Benign prostatic hyperplasia                          |                   |  |  |
| subjects affected / exposed                           | 4 / 110 (3.64%)   |  |  |
| occurrences (all)                                     | 4                 |  |  |
| Gastrointestinal disorders                            |                   |  |  |
| Diarrhoea   |                   |  |  |
| subjects affected / exposed                           | 4 / 110 (3.64%)   |  |  |
| occurrences (all)                                     | 4                 |  |  |
| Musculoskeletal and connective tissue disorders       |                   |  |  |
| Arthralgia  |                   |  |  |
| subjects affected / exposed                           | 5 / 110 (4.55%)   |  |  |
| occurrences (all)                                     | 5                 |  |  |
| Infections and infestations                           |                   |  |  |
| Urinary tract infection                               |                   |  |  |
| subjects affected / exposed                           | 8 / 110 (7.27%)   |  |  |
| occurrences (all)                                     | 11                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 16 September 2019 | <p>Amendment 1 included the following changes:</p> <ul style="list-style-type: none"><li>• Extended study from 26 weeks to 182 weeks</li><li>• Added assigned EudraCT number</li><li>• Added new Clinical Study Director</li><li>• Increased the number of countries from 20 to 25</li><li>• Changed visit designation from days to weeks for ease of reference</li><li>• Removed the requirement to discuss discontinuation of participants with the Sponsor's medical monitor to comply with ethics committee standards</li><li>• Added clarification of the variable assessments in the first 26 weeks vs. the remaining 158 weeks</li><li>• Made the wording concise in exclusion criteria</li><li>• Added allowance for participants to be concurrently enrolled in observational studies</li><li>• Deleted language that was not relevant to this study (there were no "predose" requirements; all participants rolled over from previous study)</li><li>• Added table for study extension visits</li><li>• Updated to provide clarification of the variable assessments in the first 26 weeks vs. the remaining 158 weeks</li><li>• Provided rationale for extending the study for an additional 3 years</li><li>• Changed language for "Exploratory Endpoint"</li><li>• Clarified this was an open-label (OL) study and participants were not "randomized"</li><li>• Updated to provide clarification of what assessments were done if a participant terminated the study prior to Week 26</li><li>• Added the 3-year extension and detailed what assessments were done at visits after Visit 6</li><li>• Provided clarification regarding cannabinoid usage to comply with regulations in countries/states where cannabinoid use was not legal</li><li>• Changed "1 month" to "30 days" for consistency with previous studies within the program.</li></ul> |

|                |  |
|----------------|--|
| 05 August 2020 | <p>Amendment 2, included the following non-administrative changes:</p> <ul style="list-style-type: none"> <li>• Added study and drug name and name of the new Clinical Study Director; references to "snOH" were changed to "symptomatic nOH" to clearly define disease under study and consistency throughout the document</li> <li>• Study design updated for the implementation of the Decentralized Platform in response to the COVID-19 pandemic</li> <li>• Clarification and elaboration that the number of participants in this study was based upon the number of participants completing Study 0170, and the anticipated incidence of syncopal and hypertensive events driven by this enrollment number</li> <li>• Re-ordered procedures for consistency with other amprelosetine protocols 0169 and 0170</li> <li>• Study 0145 was completed, and the results were presented in the protocol; clarified with more recent information regarding study status</li> <li>• Clarified where study visits could be conducted along with the inclusion of unscheduled visits</li> <li>• Introduced the Study Reference Manual as source</li> <li>• Additional instructions provided regarding the conduct of remote and in-clinic study visits and where reader could find additional details</li> <li>• Provided clarity on the optimal time(s) protocol procedures should be conducted</li> <li>• Removed statement regarding timing of ECG</li> <li>• Added information and instructions regarding the Unscheduled Visit</li> <li>• Maintaining a constant smoking habit was not required</li> <li>• Clarified that participants would be discontinued from the study in addition to stopping study medication if a stopping criterion was met</li> <li>• Contact information for medical monitoring was updated for coverage of Latin America sites</li> <li>• This was a safety study, and no efficacy data were analyzed</li> <li>• Introduction of statistical group providing support for IDMC</li> <li>• Updated principal investigator responsibility to include oversight of home health provider working with the site</li> <li>• Added additional information regarding electronic clinical outcome assessment data collection.</li> </ul> |
|----------------|--|

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Because the study was terminated early by the Sponsor, the latest scheduled study visit completed by any participant was at Week 98.

Notes: