

**Clinical trial results:****A Phase 3, 22-week, Multi-center, Randomized Withdrawal Study of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension in Subjects with Primary Autonomic Failure****Summary**

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2018-003941-41 |
| Trial protocol | GB EE PL ES AT DK BG HU PT IT |
| Global end of trial date | 10 November 2021 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 23 February 2023 |
| First version publication date | 15 December 2022 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data setEdits to the primary endpoint description. |

Trial information**Trial identification**

| | |
|-----------------------|------|
| Sponsor protocol code | 0170 |
|-----------------------|------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03829657 |
| 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 | Brett Haumann, Theravance Biopharma Ireland Limited, 00 35315394800, bhaumann@theravance.com |
| Scientific contact | Brett Haumann, Theravance Biopharma Ireland Limited, 00 35315394800, bhaumann@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 | 10 November 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 November 2021 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the durability of effect of amprelosetine in participants with symptomatic neurogenic orthostatic hypotension (symptomatic nOH) due to multiple system atrophy (MSA), Parkinson's disease (PD), or pure autonomic failure (PAF) compared with placebo over a double-blind, randomized withdrawal (RW) period of 6 weeks following an open label (OL) treatment of 16 weeks.

To evaluate the safety and tolerability of amprelosetine when taken for up to 22 weeks.

Protection of trial subjects:

This trial 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 | 22 February 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 | Austria: 1 |
| Country: Number of subjects enrolled | Estonia: 4 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Poland: 25 |
| Country: Number of subjects enrolled | Australia: 7 |
| Country: Number of subjects enrolled | Canada: 5 |
| Country: Number of subjects enrolled | Israel: 4 |
| Country: Number of subjects enrolled | New Zealand: 3 |
| Country: Number of subjects enrolled | United States: 50 |
| Country: Number of subjects enrolled | Germany: 9 |
| Country: Number of subjects enrolled | Italy: 16 |
| Country: Number of subjects enrolled | Bulgaria: 6 |
| Country: Number of subjects enrolled | Spain: 9 |
| Country: Number of subjects enrolled | Denmark: 2 |
| Country: Number of subjects enrolled | Hungary: 3 |
| Country: Number of subjects enrolled | Portugal: 3 |
| Country: Number of subjects enrolled | Russian Federation: 14 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Ukraine: 21 |
| Country: Number of subjects enrolled | United Kingdom: 18 |
| Worldwide total number of subjects | 203 |
| EEA total number of subjects | 81 |

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) | 203 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled from February 2019 to November 2021.

Pre-assignment

Screening details:

203 participants were enrolled in the OL treatment period and 128 participants who completed the OL treatment period continued in the RW treatment period.

Period 1

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

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | OL Treatment Period: 0169 Placebo Rollover |

Arm description:

Participants who received the placebo in study 0169, received 10 mg oral ampreloxetine once a day (QD) for up to 16 weeks.

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

Dosage and administration details:

Participants received 10 mg QD for up to 16 weeks.

| | |
|------------------|---|
| Arm title | OL Treatment Period: 0169 Ampreloxetine |
|------------------|---|

Arm description:

Participants who received ampreloxetine in study 0169, received 10 mg oral ampreloxetine QD for up to 16 weeks.

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

Dosage and administration details:

Participants received 10 mg QD for up to 16 weeks.

| | |
|------------------|------------------------------|
| Arm title | OL Treatment Period: De Novo |
|------------------|------------------------------|

Arm description:

Participants with symptomatic neurogenic orthostatic hypotension (nOH) who met all applicable study inclusion criteria and none of the applicable exclusion criteria, received 10 mg oral ampreloxetine QD for up to 16 weeks. These participants did not roll over from the 0169 study.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|---------------|
| Investigational medicinal product name | Ampreloxetine |
| Investigational medicinal product code | |
| Other name | TD-9855 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 10 mg QD for up to 16 weeks.

| Number of subjects in period 1 | OL Treatment Period: 0169 Placebo Rollover | OL Treatment Period: 0169 Ampreloxetine | OL Treatment Period: De Novo |
|---|--|---|------------------------------|
| Started | 85 | 85 | 33 |
| Completed | 52 | 64 | 12 |
| Not completed | 33 | 21 | 21 |
| Consent withdrawn by subject | 6 | 7 | 5 |
| Physician decision | 1 | - | - |
| Adverse event, non-fatal | 12 | 4 | 2 |
| Miscellaneous | 3 | 1 | 1 |
| Failure to Meet Day 29 Continuation Criterion | 10 | 6 | 4 |
| Study Terminated by Sponsor | 1 | 3 | 9 |

Period 2

| | |
|------------------------------|--|
| Period 2 title | RW Treatment Period (Week 16 to Week 24) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Carer, Subject |

Arms

| | |
|------------------------------|------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | RW Treatment Period: Placebo |

Arm description:

Participants who completed the OL treatment period and were randomized to receive oral placebo QD for a further 6 weeks in the RW treatment period.

| | |
|--|----------|
| 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:

Participants received the placebo QD for a further 6 weeks.

| | |
|------------------|------------------------------------|
| Arm title | RW Treatment Period: Ampreloxetine |
|------------------|------------------------------------|

Arm description:

Participants who completed the OL treatment period and were randomized to receive 10 mg oral ampreloxetine QD for a further 6 weeks in the RW treatment period.

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

Dosage and administration details:

Participants received 10 mg QD for a further 6 weeks.

| Number of subjects in period 2 | RW Treatment Period: Placebo | RW Treatment Period: Ampreloxetine |
|---------------------------------------|------------------------------|------------------------------------|
| | | |
| Started | 64 | 64 |
| Completed | 61 | 58 |
| Not completed | 3 | 6 |
| Consent withdrawn by subject | 1 | 1 |
| Adverse event, non-fatal | - | 1 |
| Miscellaneous | - | 1 |
| Study Terminated by Sponsor | 2 | 3 |

Baseline characteristics

Reporting groups

| | |
|--|--|
| Reporting group title | OL Treatment Period: 0169 Placebo Rollover |
| Reporting group description: Participants who received the placebo in study 0169, received 10 mg oral amprelosetine once a day (QD) for up to 16 weeks. | |
| Reporting group title | OL Treatment Period: 0169 Amprelosetine |
| Reporting group description: Participants who received amprelosetine in study 0169, received 10 mg oral amprelosetine QD for up to 16 weeks. | |
| Reporting group title | OL Treatment Period: De Novo |
| Reporting group description: Participants with symptomatic neurogenic orthostatic hypotension (nOH) who met all applicable study inclusion criteria and none of the applicable exclusion criteria, received 10 mg oral amprelosetine QD for up to 16 weeks. These participants did not roll over from the 0169 study. | |

| Reporting group values | OL Treatment Period: 0169 Placebo Rollover | OL Treatment Period: 0169 Amprelosetine | OL Treatment Period: De Novo |
|---|--|---|------------------------------|
| Number of subjects | 85 | 85 | 33 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous | | | |
| OL Treatment Period Safety Analysis Set: all enrolled participants who received at least 1 dose of amprelosetine during the OL period. 3 participants are not included in the analysis and the N value = 200. 0169 Placebo Rollover N = 83 0169 Amprelosetine Rollover N = 85 De Novo N = 32 | | | |
| Units: years arithmetic mean standard deviation | 68.2 ± 9.35 | 68.2 ± 9.00 | 69.0 ± 7.97 |
| Gender categorical Units: Subjects | | | |
| Female | 22 | 30 | 8 |
| Male | 61 | 55 | 24 |
| Not Reported | 2 | 0 | 1 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 2 | 4 | 0 |

| | | | |
|-----------------------------------|----|----|----|
| Not Hispanic or Latino | 77 | 76 | 32 |
| Unknown or Not Reported | 6 | 5 | 1 |
| Race/Ethnicity Units: Subjects | | | |
| White | 80 | 83 | 31 |
| Black or African American | 0 | 1 | 1 |
| Asian | 2 | 1 | 0 |
| Other | 1 | 0 | 0 |
| Not Reported | 2 | 0 | 1 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 203 | | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| OL Treatment Period Safety Analysis Set: all enrolled participants who received at least 1 dose of amprelosetine during the OL period. 3 participants are not included in the analysis and the N value = 200. 0169 Placebo Rollover N = 83 0169 Amprelosetine Rollover N = 85 De Novo N = 32 | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 60 | | |
| Male | 140 | | |
| Not Reported | 3 | | |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 6 | | |
| Not Hispanic or Latino | 185 | | |
| Unknown or Not Reported | 12 | | |
| Race/Ethnicity Units: Subjects | | | |
| White | 194 | | |
| Black or African American | 2 | | |
| Asian | 3 | | |
| Other | 1 | | |
| Not Reported | 3 | | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | OL Treatment Period: 0169 Placebo Rollover |
| Reporting group description: Participants who received the placebo in study 0169, received 10 mg oral ampreloxetine once a day (QD) for up to 16 weeks. | |
| Reporting group title | OL Treatment Period: 0169 Ampreloxetine |
| Reporting group description: Participants who received ampreloxetine in study 0169, received 10 mg oral ampreloxetine QD for up to 16 weeks. | |
| Reporting group title | OL Treatment Period: De Novo |
| Reporting group description: Participants with symptomatic neurogenic orthostatic hypotension (nOH) who met all applicable study inclusion criteria and none of the applicable exclusion criteria, received 10 mg oral ampreloxetine QD for up to 16 weeks. These participants did not roll over from the 0169 study. | |
| Reporting group title | RW Treatment Period: Placebo |
| Reporting group description: Participants who completed the OL treatment period and were randomized to receive oral placebo QD for a further 6 weeks in the RW treatment period. | |
| Reporting group title | RW Treatment Period: Ampreloxetine |
| Reporting group description: Participants who completed the OL treatment period and were randomized to receive 10 mg oral ampreloxetine QD for a further 6 weeks in the RW treatment period. | |

Primary: Proportion of Treatment Failure at Week 6 of RW Treatment Period

| | |
|---|--|
| End point title | Proportion of Treatment Failure at Week 6 of RW Treatment Period |
| End point description: Treatment failure was defined as proportion of participants who met the following criteria at Week 6 following randomization: Change (worsening) from baseline in Question 1 of the Orthostatic Hypotension Symptom Assessment (OHSA#1) score of 1.0 point and worsening of disease severity as assessed by a 1-point change in Patient Global Impression of Severity (PGI-S). OHSA Question #1 assessed dizziness, lightheadedness, feeling faint, or feeling like you might blackout. PGI-S assessed patient's impression of disease severity. Least squares mean is the model-based proportion of participants with treatment failure using logistic regression. RW Treatment Period Full Analysis Set: all randomized participants who received at least 1 dose of study medication (ampreloxetine or placebo) following randomization. | |
| End point type | Primary |
| End point timeframe: 6-week randomized withdrawal period (Week 16 to Week 22) | |

| End point values | RW Treatment Period: Placebo | RW Treatment Period: Ampreloxetine | | |
|--|------------------------------|------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 64 | 64 | | |
| Units: Proportion of treatment failure | | | | |
| least squares mean (standard error) | 0.42 (± 0.068) | 0.30 (± 0.065) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Placebo vs Amprexetine |
| Comparison groups | RW Treatment Period: Placebo v RW Treatment Period: Amprexetine |
| Number of subjects included in analysis | 128 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.196 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.27 |
| upper limit | 1.29 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

OL Treatment Period: Day 1 to Week 16 (plus a 2 week follow-up period); RW Treatment Period: Week 16 to Week 24 (plus a 2 week follow-up period)

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | OL Treatment Period |
|-----------------------|---------------------|

Reporting group description:

Includes all participants in the OL treatment period. Participants received 10 mg oral amprelosetine once a day (QD) for up to 16 weeks.

| | |
|-----------------------|------------------------------|
| Reporting group title | RW Treatment Period: Placebo |
|-----------------------|------------------------------|

Reporting group description:

Participants who completed the OL treatment period and were randomized to receive oral placebo QD for a further 6 weeks in the RW treatment period.

| | |
|-----------------------|------------------------------------|
| Reporting group title | RW Treatment Period: Amprelosetine |
|-----------------------|------------------------------------|

Reporting group description:

Participants who completed the OL treatment period and were randomized to receive 10 mg oral amprelosetine QD for a further 6 weeks in the RW treatment period.

| Serious adverse events | OL Treatment Period | RW Treatment Period: Placebo | RW Treatment Period: Amprelosetine |
|---|---------------------|------------------------------|------------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 200 (8.00%) | 2 / 64 (3.13%) | 4 / 64 (6.25%) |
| number of deaths (all causes) | 5 | 0 | 2 |
| number of deaths resulting from adverse events | 0 | 0 | 1 |
| Injury, poisoning and procedural complications | | | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Hip fracture | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Injury | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Spinal column injury | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 1 / 64 (1.56%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Atrioventricular block | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Surgical and medical procedures | | | |
| Hip arthroplasty | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 |

| | | | |
|--|-----------------|----------------|----------------|
| Nervous system disorders | | | |
| Bulbar palsy | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Neurological decompensation | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Parkinson's disease | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 | | | |
| Subcapsular renal haematoma | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 | | | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | OL Treatment Period | RW Treatment Period: Placebo | RW Treatment Period: Amprexetine |
|--|----------------------|------------------------------|----------------------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 105 / 200 (52.50%) | 16 / 64 (25.00%) | 17 / 64 (26.56%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Haemangioma subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Vascular disorders Diastolic hypertension subjects affected / exposed occurrences (all) | 0 / 200 (0.00%) 0 | 1 / 64 (1.56%) 1 | 0 / 64 (0.00%) 0 |
| Flushing subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Hot flush subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Hypertension subjects affected / exposed occurrences (all) | 2 / 200 (1.00%) 3 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Hypotension subjects affected / exposed occurrences (all) | 0 / 200 (0.00%) 0 | 1 / 64 (1.56%) 1 | 0 / 64 (0.00%) 0 |
| Orthostatic hypotension subjects affected / exposed occurrences (all) | 2 / 200 (1.00%) 3 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Supine hypertension subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| White coat hypertension | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Discomfort | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | 0 / 64 (0.00%) | 2 / 64 (3.13%) |
| occurrences (all) | 2 | 0 | 2 |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Malaise | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 200 (1.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Pain | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pyrexia | | | |

| | | | |
|---|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 3 / 200 (1.50%) 3 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Immune system disorders Allergy to vaccine subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Seasonal allergy subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Social circumstances Walking disability subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Reproductive system and breast disorders Endometrial hyperplasia subjects affected / exposed occurrences (all) | 0 / 200 (0.00%) 0 | 1 / 64 (1.56%) 1 | 0 / 64 (0.00%) 0 |
| Gynaecomastia subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Ovarian cyst subjects affected / exposed occurrences (all) | 0 / 200 (0.00%) 0 | 1 / 64 (1.56%) 1 | 0 / 64 (0.00%) 0 |
| Priapism subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Uterine enlargement subjects affected / exposed occurrences (all) | 0 / 200 (0.00%) 0 | 1 / 64 (1.56%) 1 | 0 / 64 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Dyspnoea subjects affected / exposed occurrences (all) | 2 / 200 (1.00%) 2 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| Epistaxis | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Anxiety | | | |
| subjects affected / exposed | 3 / 200 (1.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Bruxism | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Confusional state | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed | 3 / 200 (1.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Hallucination | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Hallucination, visual | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypomania | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 3 / 200 (1.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Mental status changes | | | |

| | | | |
|--|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Panic attack subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Sleep disorder subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Product issues Device occlusion subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 2 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Investigations Post procedural discomfort subjects affected / exposed occurrences (all) | 0 / 200 (0.00%) 0 | 1 / 64 (1.56%) 2 | 0 / 64 (0.00%) 0 |
| Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 3 / 200 (1.50%) 3 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 2 / 200 (1.00%) 2 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Blood pressure increased subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Blood urea increased subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Colonoscopy subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Cystoscopy | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 200 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Glomerular filtration rate abnormal | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Glomerular filtration rate decreased | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haematocrit decreased | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Troponin increased | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Back injury | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Contusion | | | |
| subjects affected / exposed | 3 / 200 (1.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Fall | | | |
| subjects affected / exposed | 3 / 200 (1.50%) | 1 / 64 (1.56%) | 1 / 64 (1.56%) |
| occurrences (all) | 3 | 1 | 1 |
| Hand fracture | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Limb injury | | | |

| | | | |
|--|-----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 200 (0.00%) 0 | 0 / 64 (0.00%) 0 | 1 / 64 (1.56%) 1 |
| Skin laceration subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Soft tissue injury subjects affected / exposed occurrences (all) | 0 / 200 (0.00%) 0 | 0 / 64 (0.00%) 0 | 1 / 64 (1.56%) 1 |
| Cardiac disorders Atrioventricular block first degree subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Bundle branch block left subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Myocardial infarction subjects affected / exposed occurrences (all) | 0 / 200 (0.00%) 0 | 1 / 64 (1.56%) 2 | 0 / 64 (0.00%) 0 |
| Tachycardia subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Nervous system disorders Balance disorder subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Burning sensation subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Dizziness subjects affected / exposed occurrences (all) | 7 / 200 (3.50%) 13 | 1 / 64 (1.56%) 1 | 2 / 64 (3.13%) 2 |
| Dizziness exertional subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Dizziness postural | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 7 | 0 | 0 |
| Dyskinesia | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 8 / 200 (4.00%) | 2 / 64 (3.13%) | 0 / 64 (0.00%) |
| occurrences (all) | 14 | 6 | 0 |
| Hypokinesia | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Memory impairment | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Migraine with aura | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Multiple system atrophy | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| On and off phenomenon | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Oromandibular dystonia | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Parkinson's disease | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Presyncope | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 1 | 0 | 1 |
| Radial nerve palsy | | | |

| | | | |
|--------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Radiculopathy | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Spasmodic dysphonia | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Speech disorder | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Syncope | | | |
| subjects affected / exposed | 4 / 200 (2.00%) | 0 / 64 (0.00%) | 2 / 64 (3.13%) |
| occurrences (all) | 4 | 0 | 2 |
| Tremor | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bulbar palsy | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 200 (1.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Anaemia vitamin B12 deficiency | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lymphopenia | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |

| | | | |
|----------------------------------|-----------------|----------------|----------------|
| Eye disorders | | | |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Diplopia | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypermetropia | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Open angle glaucoma | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Vitreous floaters | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 6 / 200 (3.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 6 | 0 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 1 | 0 | 1 |
| Dry mouth | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 1 | 0 | 1 |
| Inguinal hernia | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Large intestine polyp | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 7 / 200 (3.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 7 | 0 | 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Retching | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Erythema | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hair growth rate abnormal | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hand dermatitis | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyperhidrosis | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 4 / 200 (2.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 4 | 0 | 1 |
| Palmar erythema | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 3 / 200 (1.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 3 / 200 (1.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Rash pruritic | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal and urinary disorders | | | |
| Calculus bladder | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Calculus urinary | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haematuria | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nocturia | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urinary hesitation | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences (all) | 1 | 0 | 1 |

| | | | |
|---|-----------------|----------------|----------------|
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Back pain | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Groin pain | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Joint swelling | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Mobility decreased | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Osteoporosis | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Tendonitis | | | |

| | | | |
|--|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 1 / 64 (1.56%) | 1 / 64 (1.56%) |
| occurrences (all) | 0 | 1 | 1 |
| COVID-19 | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 200 (1.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pharyngitis streptococcal | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tooth abscess | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 200 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 12 / 200 (6.00%) | 3 / 64 (4.69%) | 2 / 64 (3.13%) |
| occurrences (all) | 17 | 3 | 3 |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | 0 / 64 (0.00%) | 0 / 64 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|----------------------|---------------------|---------------------|
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 2 / 200 (1.00%) 2 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 0 / 64 (0.00%) 0 | 0 / 64 (0.00%) 0 |
| Vitamin D deficiency subjects affected / exposed occurrences (all) | 1 / 200 (0.50%) 1 | 1 / 64 (1.56%) 1 | 0 / 64 (0.00%) 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 04 March 2019 | <ul style="list-style-type: none">• Added the new drug name• Updated the number of countries• Increased the screening window to allow adequate time for NE sample processing• Updated the number of days in the screening period from 14 days (2 weeks) to 21 days (3 weeks) to allow adequate time for norepinephrine (NE) sample processing• Clarified and defined "sustained" in regard to systolic blood pressure (SBP) for at least 4 hours after 3 minutes of standing or after 5 minutes in the sitting position• Added 'becoming pregnant' as one of the stopping rules• Included a detailed description of highly acceptable methods of contraception including definition of sexual abstinence• Correction made in regard to diagnostic criteria• Made the wording concise in exclusion criteria• Removed specific OH medications• Removed the requirement that study medication must be taken "prior to breakfast"• Removed the requirement to contact the Sponsor prior to unblinding a participant's treatment• Clarified and defined acceptable contraception methods• Limited potential weight variations due to external factors like type of clothing etc.• Allowed fludrocortisone and cannabinoids• Prohibited the use of NE reuptake inhibitor (NRIs), NSRIs, serotonin norepinephrine reuptake inhibitors (SNRIs), and psychostimulants• Updated the PGI-S to a 5-category scale• Removed reference to specific device (Kinesia 360)• Made language around assessments more generic• Allowed for possibility that some countries could not import the device |

| | |
|------------------|--|
| 04 December 2019 | <ul style="list-style-type: none"> • Added study name • Changed personnel • Added additional sites and countries • Provided clarification that, apart from primary and key secondary objectives, other objectives were now classified explicitly as exploratory • Increased screening period to allow sufficient time for conduct of screening procedures • Removed requirement of discussion with Sponsor's medical monitor • Extended screening window to 4 weeks, other corresponding changes • Clarified diagnosis of PAF • Allowed enrollment of participant's with controlled diabetes mellitus • Droxidopa was not available in all countries where the trial was conducted; thus, only if applicable • Excluded participants with hypersensitivity to ampreloxetine • Added continuation criteria to synopsis • Prohibited alpha blockers • Clarified efficacy endpoints • Clarified the statistical testing procedure as discussed in detail in statistical analysis plan (SAP) • Improved wording • Provided clearer instructions on conduct of corresponding study procedures • Added terms for completeness • Clarified Study 0145 was completed and results were presented in protocol • Clarified the optimal time(s) protocol procedures should be conducted • Allowed for a confirmation if there was doubt per Investigator's opinion • Clarification procedure conduct • Clarified the need for additional testing if the participant had diabetes mellitus • Provide clarification of the chemistry panel • Removed involvement of Sponsor should the Investigator decide to withdraw a participant from the study |
| 20 March 2020 | <ul style="list-style-type: none"> • Additional electrocardiogram (ECG) added as a safety measure • Provided clarification on ECG completion duration • Clarified language and updated text to reflect internal standards |
| 05 August 2020 | <ul style="list-style-type: none"> • Added study and drug name and name of the new Clinical Study Director • References to "snOH" changed to "symptomatic nOH" to clearly define disease under study and consistency throughout the document • Clarified references for consistency throughout the document to differentiate those that had signed study informed consent form • Clarified that Study 0145 was completed and results were presented in the protocol • Stated reasoning for update in study design, which was the implementation of the Decentralized Platform in response to the COVID-19 pandemic • Clarified the screening visit must be performed in clinic • Clarified the role of the Engineering Steering Committee and their decision-making process • Added exclusion for SARS-CoV-2 infection due to COVID-19 pandemic • Clarity added, and order revised for consistency across the document, and to reflect the removal of smoking status subgroups in the SAP • Added baseline NE subgroups • Changed the postbaseline blood sample collection time point for pharmacodynamic markers (NR and dihydroxyphenylglycol) from Day 29 to Day 57 • To the planned analyses of standing SBP at 3 minutes and at 10 minutes during the orthostatic standing test, addition of similar analyses of standing heart rate at 3 minutes and at 10 minutes. |

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.

De Novo participants in the OL treatment period had limited follow-up due to early termination of the study.

Notes: