

**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"><li>• Correction of full data set</li><li>Edits to the primary endpoint description.</li></ul>

**Trial information****Trial identification**

Sponsor protocol code	0170
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**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:

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**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
<b>Arm title</b>	OL Treatment Period: 0169 Placebo Rollover

Arm description:

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

Arm type	Experimental
Investigational medicinal product name	Amprelosetine
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.

<b>Arm title</b>	OL Treatment Period: 0169 Amprelosetine
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Arm description:

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

Arm type	Experimental
Investigational medicinal product name	Amprelosetine
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.

<b>Arm title</b>	OL Treatment Period: De Novo
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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 amprelosetine QD for up to 16 weeks. These participants did not roll over from the 0169 study.

Arm type	Experimental
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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
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
<b>Arm title</b>	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.

<b>Arm title</b>	RW Treatment Period: Ampreloxetine
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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.

<b>Number of subjects in period 2</b>	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 Male Not Reported	22 61 2	30 55 0	8 24 1
Ethnicity Units: Subjects			
Hispanic or Latino	2	4	0

Not Hispanic or Latino	77	76	32
Unknown or Not Reported	6	5	1
<b>Race/Ethnicity</b>			
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

<b>Reporting group values</b>	Total		
Number of subjects	203		
<b>Age categorical</b>			
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		
<b>Age continuous</b>			
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			
<b>Units: years</b>			
arithmetic mean			
standard deviation	-		
<b>Gender categorical</b>			
Units: Subjects			
Female	60		
Male	140		
Not Reported	3		
<b>Ethnicity</b>			
Units: Subjects			
Hispanic or Latino	6		
Not Hispanic or Latino	185		
Unknown or Not Reported	12		
<b>Race/Ethnicity</b>			
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 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 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.	

### 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 (amprelosetine 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: Amprelosetine		
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

<b>Statistical analysis title</b>	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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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### Reporting groups

Reporting group title	OL Treatment Period
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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
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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
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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.

<b>Serious adverse events</b>	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
<b>Spinal column injury</b>			
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
<b>Vascular disorders</b>			
<b>Orthostatic hypotension</b>			
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
<b>Cardiac disorders</b>			
<b>Atrial flutter</b>			
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
<b>Atrioventricular block</b>			
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
<b>Bradycardia</b>			
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
<b>Myocardial infarction</b>			
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
<b>Surgical and medical procedures</b>			
<b>Hip arthroplasty</b>			
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
<b>Respiratory failure</b>			
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
<b>Musculoskeletal and connective tissue disorders</b>			
<b>Pain in extremity</b>			
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
<b>Infections and infestations</b>			
<b>COVID-19</b>			
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
<b>Pneumonia</b>			
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
<b>Pneumonia aspiration</b>			
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
<b>Respiratory tract infection</b>			
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
<b>Urinary tract infection</b>			
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 %

<b>Non-serious adverse events</b>	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 occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 64 (1.56%) 1	0 / 64 (0.00%) 0
Chest pain			
subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
Discomfort			
subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
Fatigue			
subjects affected / exposed occurrences (all)	2 / 200 (1.00%) 2	0 / 64 (0.00%) 0	2 / 64 (3.13%) 2
Gait disturbance			
subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	1 / 64 (1.56%) 1	0 / 64 (0.00%) 0
Hyperthermia			
subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 64 (1.56%) 1	0 / 64 (0.00%) 0
Malaise			
subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
Oedema peripheral			
subjects affected / exposed occurrences (all)	3 / 200 (1.50%) 3	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
Pain			
subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
Peripheral swelling			
subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 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	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Seasonal allergy			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Social circumstances			
Walking disability			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 64 (1.56%)	0 / 64 (0.00%)
occurrences (all)	0	1	0
Gynaecomastia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Ovarian cyst			
subjects affected / exposed	0 / 200 (0.00%)	1 / 64 (1.56%)	0 / 64 (0.00%)
occurrences (all)	0	1	0
Priapism			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Uterine enlargement			
subjects affected / exposed	0 / 200 (0.00%)	1 / 64 (1.56%)	0 / 64 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	2 / 200 (1.00%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	2	0	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
<b>Radiculopathy</b>			
subjects affected / exposed	0 / 200 (0.00%)	0 / 64 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	0	1
<b>Restless legs syndrome</b>			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
<b>Somnolence</b>			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
<b>Spasmodic dysphonia</b>			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
<b>Speech disorder</b>			
subjects affected / exposed	1 / 200 (0.50%)	1 / 64 (1.56%)	0 / 64 (0.00%)
occurrences (all)	1	1	0
<b>Syncope</b>			
subjects affected / exposed	4 / 200 (2.00%)	0 / 64 (0.00%)	2 / 64 (3.13%)
occurrences (all)	4	0	2
<b>Tremor</b>			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
<b>Bulbar palsy</b>			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
<b>Blood and lymphatic system disorders</b>			
<b>Anaemia</b>			
subjects affected / exposed	3 / 200 (1.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	3	0	0
<b>Anaemia vitamin B12 deficiency</b>			
subjects affected / exposed	0 / 200 (0.00%)	1 / 64 (1.56%)	0 / 64 (0.00%)
occurrences (all)	0	1	0
<b>Lymphopenia</b>			
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 occurrences (all)	4 / 200 (2.00%) 4	0 / 64 (0.00%) 0	1 / 64 (1.56%) 1
Palmar erythema subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	3 / 200 (1.50%) 3	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	3 / 200 (1.50%) 3	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
Rash pruritic subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
Renal and urinary disorders			
Calculus bladder subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	0 / 64 (0.00%) 0	1 / 64 (1.56%) 1
Calculus urinary subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
Haematuria subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
Nocturia subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
Pollakiuria subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
Urinary hesitation subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
Urinary retention subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	1 / 64 (1.56%) 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
<b>Infections and infestations</b>			
<b>Bronchitis</b>			
subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 64 (1.56%) 1	1 / 64 (1.56%) 1
<b>COVID-19</b>			
subjects affected / exposed occurrences (all)	2 / 200 (1.00%) 2	1 / 64 (1.56%) 1	0 / 64 (0.00%) 0
<b>Conjunctivitis</b>			
subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
<b>Nasopharyngitis</b>			
subjects affected / exposed occurrences (all)	3 / 200 (1.50%) 3	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
<b>Oral candidiasis</b>			
subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
<b>Pharyngitis streptococcal</b>			
subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
<b>Rhinitis</b>			
subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
<b>Tooth abscess</b>			
subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 0
<b>Upper respiratory tract infection</b>			
subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 64 (1.56%) 1	0 / 64 (0.00%) 0
<b>Urinary tract infection</b>			
subjects affected / exposed occurrences (all)	12 / 200 (6.00%) 17	3 / 64 (4.69%) 3	2 / 64 (3.13%) 3
<b>Urinary tract infection bacterial</b>			
subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 64 (0.00%) 0	0 / 64 (0.00%) 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"><li>• Added the new drug name</li><li>• Updated the number of countries</li><li>• Increased the screening window to allow adequate time for NE sample processing</li><li>• 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</li><li>• 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</li><li>• Added 'becoming pregnant' as one of the stopping rules</li><li>• Included a detailed description of highly acceptable methods of contraception including definition of sexual abstinence</li><li>• Correction made in regard to diagnostic criteria</li><li>• Made the wording concise in exclusion criteria</li><li>• Removed specific OH medications</li><li>• Removed the requirement that study medication must be taken "prior to breakfast"</li><li>• Removed the requirement to contact the Sponsor prior to unblinding a participant's treatment</li><li>• Clarified and defined acceptable contraception methods</li><li>• Limited potential weight variations due to external factors like type of clothing etc.</li><li>• Allowed fludrocortisone and cannabinoids</li><li>• Prohibited the use of NE reuptake inhibitor (NRIs), NSRIs, serotonin norepinephrine reuptake inhibitors (SNRIs), and psychostimulants</li><li>• Updated the PGI-S to a 5-category scale</li><li>• Removed reference to specific device (Kinesia 360)</li><li>• Made language around assessments more generic</li><li>• Allowed for possibility that some countries could not import the device</li></ul>

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

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

Notes: