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	• Correction of full data set Edits 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 ampreloxetine 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 ampreloxetine 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 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 values	OL Treatment Period: 0169 Placebo Rollover	OL Treatment Period: 0169 Ampreloxetine	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 ampreloxetine during the OL period. 3 participants are not included in the analysis and the N value = 200. 0169 Placebo Rollover N = 83 0169 Ampreloxetine Rollover N = 85 De Novo N = 32			
Units: years			
arithmetic mean	68.2	68.2	69.0
standard deviation	± 9.35	± 9.00	± 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 ampreloxetine during the OL period. 3 participants are not included in the analysis and the N value = 200. 0169 Placebo Rollover N = 83 0169 Ampreloxetine 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 Ampreloxetine
Comparison groups	RW Treatment Period: Placebo v RW Treatment Period: Ampreloxetine
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 ampreloxetine 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: 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.	

Serious adverse events	OL Treatment Period	RW Treatment Period: Placebo	RW Treatment Period: Ampreloxetine
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: Ampreloxetine
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	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Diastolic hypertension			
subjects affected / exposed	0 / 200 (0.00%)	1 / 64 (1.56%)	0 / 64 (0.00%)
occurrences (all)	0	1	0
Flushing			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Hot flush			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	2 / 200 (1.00%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	3	0	0
Hypotension			
subjects affected / exposed	0 / 200 (0.00%)	1 / 64 (1.56%)	0 / 64 (0.00%)
occurrences (all)	0	1	0
Orthostatic hypotension			
subjects affected / exposed	2 / 200 (1.00%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	3	0	0
Supine hypertension			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	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	3 / 200 (1.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	3	0	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	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Panic attack			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Sleep disorder			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Product issues			
Device occlusion			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	2	0	0
Investigations			
Post procedural discomfort			
subjects affected / exposed	0 / 200 (0.00%)	1 / 64 (1.56%)	0 / 64 (0.00%)
occurrences (all)	0	2	0
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 200 (1.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	3	0	0
Blood creatinine increased			
subjects affected / exposed	2 / 200 (1.00%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	2	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Blood urea increased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Colonoscopy			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	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	0 / 200 (0.00%)	0 / 64 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	0	1
Skin laceration			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Soft tissue injury			
subjects affected / exposed	0 / 200 (0.00%)	0 / 64 (0.00%)	1 / 64 (1.56%)
occurrences (all)	0	0	1
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Bundle branch block left			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Myocardial infarction			
subjects affected / exposed	0 / 200 (0.00%)	1 / 64 (1.56%)	0 / 64 (0.00%)
occurrences (all)	0	2	0
Tachycardia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Burning sensation			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	7 / 200 (3.50%)	1 / 64 (1.56%)	2 / 64 (3.13%)
occurrences (all)	13	1	2
Dizziness exertional			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	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	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	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	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 200 (1.00%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	2	0	0
Hyperkalaemia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Hypomagnesaemia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 64 (0.00%)	0 / 64 (0.00%)
occurrences (all)	1	0	0
Vitamin D deficiency			
subjects affected / exposed	1 / 200 (0.50%)	1 / 64 (1.56%)	0 / 64 (0.00%)
occurrences (all)	1	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2019	• 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	• 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 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	• 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	• 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: