Clinical trial results:
A Phase 3, 4-week, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension in Subjects With Primary Autonomic Failure

Summary

EudraCT number	2018-003289-15
Trial protocol	GB EE DE DK AT HU PL ES BG PT IT
Global end of trial date	21 July 2021

Results information

Result version number	v1 (current)
This version publication date	09 August 2022
First version publication date	09 August 2022

Trial information

Trial identification

Sponsor protocol code	0169

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03750552
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Theravance Biopharma
Sponsor organisation address	Connaught House, 1 Burlington Road, Dublin, Ireland, D04 C5Y6
Public contact	Medical Monitor, Theravance Biopharma Inc, +1 855 633 8479, medinfo@theravance.com
Scientific contact	Dr. Richard Graham, Theravance Biopharma Inc, +1 650 808 6000, rgraham@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	21 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of TD-9855 in participants with multiple system atrophy, Parkinson’s disease, or pure autonomic failure experiencing symptomatic neurogenic orthostatic hypotension (nOH) compared with placebo at Week 4, as measured by the change from baseline of the Orthostatic Hypotension Symptom Assessment (OHSA) Question 1 (OHSA#1) score.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 June 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	Russian Federation: 21
Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	Ukraine: 19
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	Estonia: 4
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	United States: 48
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	New Zealand: 1

Worldwide total number of subjects	195
EEA total number of subjects	78

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)	53
From 65 to 84 years	140
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

195 participants were enrolled across 76 sites in Australia, Austria, Bulgaria, Canada, Denmark, Estonia, France, Germany, Hungary, Israel, Italy, New Zealand, Poland, Portugal, Spain, Russia, Ukraine, United Kingdom and the United States.

Pre-assignment

Screening details:

Overall, 194 randomized participants received at least one dose of study drug. Eight participants from one site were excluded from all analysis sets except the Randomized Analysis Set due to data integrity concerns.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ampreloxetine

Arm description:

Participants received ampreloxetine at a dose of 10 mg once daily (QD) for 4 weeks.

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

Dosage and administration details:

Participants received an oral tablet for ingestion.

Arm title	Placebo

Arm description:

Participants received placebo QD for 4 weeks.

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 an oral tablet for ingestion.

Number of subjects in period 1	Ampreloxetine	Placebo
Started	98	97
Safety Analysis Set	96	90 [1]
Full Analysis Set	94	90 [2]
Completed	90	95
Not completed	8	2
Consent withdrawn by subject	1	1
Adverse event, non-fatal	5	1
Not specified	2	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only participants with valid data were included in this analysis set.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Only participants with valid data were included in this analysis set.

Baseline characteristics

Reporting groups	
Reporting group title	Ampreloxetine
Reporting group description:	
Participants received ampreloxetine at a dose of 10 mg once daily (QD) for 4 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo QD for 4 weeks.	

Reporting group values	Ampreloxetine	Placebo	Total
Number of subjects	98	97	195
Age categorical Units: Subjects			
< 65 years	28	25	53
≥ 65 years	70	72	142
Gender categorical Units: Subjects			
Female	37	29	66
Male	61	68	129
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	3	4
Not Hispanic or Latino	92	91	183
Unknown or Not Reported	5	3	8
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	2	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	96	94	190
More than one race	0	1	1

End points

End points reporting groups

Reporting group title	Ampreloxetine
Reporting group description:	
Participants received ampreloxetine at a dose of 10 mg once daily (QD) for 4 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo QD for 4 weeks.	

Primary: Change From Baseline in Orthostatic Hypotension Symptom Assessment (OHSA) Question #1 Score at Week 4

End point title	Change From Baseline in Orthostatic Hypotension Symptom Assessment (OHSA) Question #1 Score at Week 4

End point description:

OHSA is an assessment of the severity of symptoms from low blood pressure. OHSA is a 6 question symptom assessment scale where each question uses an 11 point scale from 0 to 10, with 0 indicating no symptoms/no interference and 10 indicating the worst possible symptoms/complete interference. Question #1 assesses dizziness, lightheadedness, feeling faint, or feeling like you might blackout.

A mean negative change from baseline indicates a better outcome.

Participants included in the Full Analysis Set, defined as all randomized participants who received at least one dose of study medication and had at least 1 post-baseline measurement of OHSA question 1, were included in this analysis.

End point type	Primary
End point timeframe:	
Baseline and Week 4	

End point values	Ampreloxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	90		
Units: Score on a scale				
least squares mean (standard error)	-1.69 (± 0.290)	-1.45 (± 0.293)		

Statistical analyses

Statistical analysis title	Ampreloxetine versus (v) Placebo
Comparison groups	Ampreloxetine v Placebo

Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.574
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	0.58
Variability estimate	Standard error of the mean
Dispersion value	0.413

Secondary: Change From Baseline in Orthostatic Hypotension Symptom Assessment (OHSA) Composite Score at Week 4

End point title	Change From Baseline in Orthostatic Hypotension Symptom Assessment (OHSA) Composite Score at Week 4

End point description:

OHSA is an assessment of the severity of symptoms from low blood pressure. OHSA is a 6 question symptom assessment scale in which the composite score uses an 11 point scale from 0 to 10, with 0 indicating no symptoms/no interference and 10 indicating the worst possible symptoms/complete interference.

A mean negative change from baseline indicates a better outcome.

Participants included in the Full Analysis Set, defined as all randomized participants who received at least one dose of study medication and had at least 1 post-baseline measurement of OHSA question 1, with a valid composite OHSA score at Week 4 were included in this analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 4

End point values	Ampreloxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	87		
Units: Score on a scale				
least squares mean (standard error)	-1.32 (± 0.200)	-1.05 (± 0.202)		

Statistical analyses

Statistical analysis title	Ampreloxetine v Placebo
Comparison groups	Ampreloxetine v Placebo

Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.331
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.84
upper limit	0.28
Variability estimate	Standard error of the mean
Dispersion value	0.284

Secondary: Change From Baseline in Orthostatic Hypotension Daily Activities Scale (OHDAS) Composite Score at Week 4

End point title	Change From Baseline in Orthostatic Hypotension Daily Activities Scale (OHDAS) Composite Score at Week 4

End point description:

OHDAS is an assessment of how low blood pressure symptoms affect daily life. OHDAS is a 4 item assessment in which the composite score uses an 11 point scale from 0 to 10, with 0 indicating no symptoms/no interference and 10 indicating the worst possible symptoms/complete interference.

A mean negative change from baseline indicates a better outcome.

Participants included in the Full Analysis Set, defined as all randomized participants who received at least one dose of study medication and had at least 1 post-baseline measurement of OHSA question 1, with a valid composite OHDAS score at Week 4 were included in this analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 4

End point values	Ampreloxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	85		
Units: Score on a scale				
least squares mean (standard error)	-1.22 (± 0.265)	-0.95 (± 0.267)		

Statistical analyses

Statistical analysis title	Ampreloxetine v Placebo
Comparison groups	Ampreloxetine v Placebo

Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.481
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	0.48
Variability estimate	Standard error of the mean
Dispersion value	0.376

Secondary: Number of Participants Who Experienced an Improvement From Baseline in Patient Global Impression of Change (PGI-C) Score at Week 4

End point title	Number of Participants Who Experienced an Improvement From Baseline in Patient Global Impression of Change (PGI-C) Score at Week 4

End point description:

PGI-C was assessed using a 5-point scale where participants were asked to compare their current condition to their condition at baseline from 1 to 5, with 1 indicating the condition is very much improved and 5 indicating the condition is very much worse. These scores were analyzed in 2 categories: better and no change/worse.

Participants included in the Full Analysis Set, defined as all randomized participants who received at least one dose of study medication and had at least 1 post-baseline measurement of Orthostatic Hypotension Symptom Assessment (OHSA) question 1, who have available data were included in this analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 4

End point values	Ampreloxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	87		
Units: participants	49	45		

Statistical analyses

Statistical analysis title	Ampreloxetine v Placebo

Statistical analysis description:

Cochran-Mantel-Haenszel was stratified by disease type.

The assumed common risk difference estimate and standard error are calculated using Mantel-Haenszel stratum weights and the Sato variance estimator. Mantel-Haenszel confidence limits are shown.

Comparison groups	Ampreloxetine v Placebo
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.74
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.17
Variability estimate	Standard error of the mean
Dispersion value	0.073

Secondary: Number of Participants Who Experienced at Least One Fall

End point title	Number of Participants Who Experienced at Least One Fall

End point description:

Participants included in the Full Analysis Set, defined as all randomized participants who received at least one dose of study medication and had at least 1 post-baseline measurement of Orthostatic Hypotension Symptom Assessment (OHSA) question 1, who have available data were included in this analysis.

End point type	Secondary

End point timeframe:

Up to Week 4

End point values	Ampreloxetine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	90		
Units: participants	33	22		

Statistical analyses

Statistical analysis title	Ampreloxetine v Placebo

Statistical analysis description:

Cochran-Mantel-Haenszel was stratified by disease type.

The assumed common risk difference estimate and standard error are calculated using Mantel-Haenszel stratum weights and the Sato variance estimator. Mantel-Haenszel confidence limits are shown.

Comparison groups	Ampreloxetine v Placebo

Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0903
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.24
Variability estimate	Standard error of the mean
Dispersion value	0.064

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 43

Adverse event reporting additional description:

Participants in the Safety Analysis set, defined as all randomized subjects who received at least 1 dose of study medication, were included in this analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Ampreloxetine

Reporting group description:

Participants received ampreloxetine at a dose of 10 mg QD for 4 weeks.

Reporting group title	Placebo

Reporting group description:

Participants received placebo QD for 4 weeks.

Serious adverse events	Ampreloxetine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 96 (4.17%)	2 / 90 (2.22%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			

subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ampreloxetine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 96 (43.75%)	38 / 90 (42.22%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal cancer			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Vascular disorders			
Supine hypertension			
subjects affected / exposed	1 / 96 (1.04%)	3 / 90 (3.33%)	
occurrences (all)	1	3	
Hypertension			
subjects affected / exposed	3 / 96 (3.13%)	0 / 90 (0.00%)	
occurrences (all)	3	0	
Orthostatic hypotension			

subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Flushing			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Hot flush			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 96 (3.13%)	1 / 90 (1.11%)	
occurrences (all)	3	1	
Asthenia			
subjects affected / exposed	1 / 96 (1.04%)	1 / 90 (1.11%)	
occurrences (all)	1	1	
Catheter site pain			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Chest discomfort			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Gait disturbance			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Illness			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Injection site pain			

subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	2	
Temperature regulation disorder			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	3 / 96 (3.13%)	1 / 90 (1.11%)	
occurrences (all)	3	1	
Anxiety			
subjects affected / exposed	2 / 96 (2.08%)	1 / 90 (1.11%)	
occurrences (all)	2	1	
Abnormal dreams			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Disorientation			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	2	
Investigations			
Blood creatinine phosphokinase increased			
subjects affected / exposed	1 / 96 (1.04%)	1 / 90 (1.11%)	
occurrences (all)	1	1	
Blood creatine increased			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Blood urea increased			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Blood urea nitrogen/creatinine ratio increased			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Crystal urine present			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Eosinophil count increased			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Gastric pH decreased			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Glomerular filtration rate decreased			

subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Lymphocyte count decreased			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Mean cell haemoglobin increased			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Mean cell volume increased			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Protein urine			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Weight increased			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
White blood cell count increased			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Neutrophil count increased			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Eye contusion			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Joint injury			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Skin abrasion			

subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Skin laceration			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Thermal burn			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 96 (5.21%)	3 / 90 (3.33%)	
occurrences (all)	6	3	
Dizziness			
subjects affected / exposed	3 / 96 (3.13%)	0 / 90 (0.00%)	
occurrences (all)	4	0	
Somnolence			
subjects affected / exposed	2 / 96 (2.08%)	0 / 90 (0.00%)	
occurrences (all)	2	0	
Amnesia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Balance disorder			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Bulbar palsy			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Depressed level of consciousness			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Dizziness postural			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Dysgeusia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	

Hypoaesthesia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Lethargy			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	2	0	
Loss of consciousness			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 96 (2.08%)	2 / 90 (2.22%)	
occurrences (all)	3	2	
Constipation			
subjects affected / exposed	1 / 96 (1.04%)	1 / 90 (1.11%)	
occurrences (all)	1	1	
Dry mouth			
subjects affected / exposed	2 / 96 (2.08%)	0 / 90 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	1 / 96 (1.04%)	1 / 90 (1.11%)	
occurrences (all)	2	1	
Abdominal discomfort			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Duodenitis			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Gastric ulcer haemorrhage			

subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Gingival bleeding			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Large intestine polyp			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Salivary hypersecretion			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 96 (1.04%)	1 / 90 (1.11%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	1 / 96 (1.04%)	1 / 90 (1.11%)	
occurrences (all)	1	1	
Pruritus			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Bladder pain			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Nephrolithiasis			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Pollakiuria			

subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Urinary retention			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Urinary tract inflammation			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Urine flow decreased			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Renal cyst			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	2 / 96 (2.08%)	1 / 90 (1.11%)	
occurrences (all)	3	1	
Arthralgia			
subjects affected / exposed	1 / 96 (1.04%)	1 / 90 (1.11%)	
occurrences (all)	1	1	
Back pain			
subjects affected / exposed	0 / 96 (0.00%)	2 / 90 (2.22%)	
occurrences (all)	0	2	
Joint swelling			
subjects affected / exposed	1 / 96 (1.04%)	1 / 90 (1.11%)	
occurrences (all)	1	1	
Muscular weakness			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Pain in extremity			

subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 96 (3.13%)	4 / 90 (4.44%)	
occurrences (all)	3	4	
Upper respiratory tract infection			
subjects affected / exposed	0 / 96 (0.00%)	2 / 90 (2.22%)	
occurrences (all)	0	2	
Bacterial disease carrier			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Cystitis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 96 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2019	Changes included: Updates to discontinuation rules, acceptable methods of contraception and unblinding.
04 March 2019	Changes included: Updates to the number of countries, Screening window, Screening period, clarification of the meaning of "sustained" in regards to systolic blood pressure and stopping rules.
04 December 2019	Change included: Updates to study name, study objectives, screening period, sponsor medical monitor discussion requirement, PAF diagnosis, enrolment criteria, Droxidopa details, exclusion criteria, prohibition of alpha blockers, Study 0145 results, optimal time(s) protocol procedures should be conducted, to allow for confirmation if there is doubt per investigators opinion, additional test needed for participants with Diabetes Mellitus, chemistry panel, sponsor involvement in participant withdrawal via investigator decision and sample screening visits.
05 August 2020	Changes included: Updates to Decentralized Platform and operational design due to COVID-19.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
25 March 2020	Recruitment was paused due to COVID-19 on 25Mar2020. Screening was resumed from the 16Apr2020 on a staggered basis based upon the assessment of the COVID-19 situation at a country, regional, and local level.	16 April 2020

Notes:

Limitations and caveats

None reported