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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	0171

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Theravance Biopharma Ireland Limited
Sponsor organisation address	Ten Earlsfort Terrace, Dublin, Ireland, D02 T380
Public contact	Richard Graham, Theravance Biopharma, +1 855 633 8479, medinfo@theravance.com
Scientific contact	Richard Graham, Theravance Biopharma, +1 855 633 8479, medinfo@theravance.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 November 2021
Is this the analysis of the primary completion data?	No

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

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 September 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

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)	31
From 65 to 84 years	78
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

Arm title	Ampreloxetine

Arm description:

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

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

Baseline characteristics

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

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

End points

End points reporting groups

Reporting group title	Ampreloxetine

Reporting group description:

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

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

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs)[1]

End point description:

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

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

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

End point type	Primary

End point timeframe:

Day 1 up to a maximum of 749 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No additional statistical analysis was prespecified for this endpoint.

End point values	Ampreloxetine			
Subject group type	Reporting group			
Number of subjects analysed	110			
Units: participants	61			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to a maximum of 749 days

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Ampreloxetine

Reporting group description:

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 September 2019	Amendment 1 included the following changes: • Extended study from 26 weeks to 182 weeks • Added assigned EudraCT number • Added new Clinical Study Director • Increased the number of countries from 20 to 25 • Changed visit designation from days to weeks for ease of reference • Removed the requirement to discuss discontinuation of participants with the Sponsor's medical monitor to comply with ethics committee standards • Added clarification of the variable assessments in the first 26 weeks vs. the remaining 158 weeks • Made the wording concise in exclusion criteria • Added allowance for participants to be concurrently enrolled in observational studies • Deleted language that was not relevant to this study (there were no "predose" requirements; all participants rolled over from previous study) • Added table for study extension visits • Updated to provide clarification of the variable assessments in the first 26 weeks vs. the remaining 158 weeks • Provided rationale for extending the study for an additional 3 years • Changed language for "Exploratory Endpoint" • Clarified this was an open-label (OL) study and participants were not "randomized" • Updated to provide clarification of what assessments were done if a participant terminated the study prior to Week 26 • Added the 3-year extension and detailed what assessments were done at visits after Visit 6 • Provided clarification regarding cannabinoid usage to comply with regulations in countries/states where cannabinoid use was not legal • Changed "1 month" to "30 days" for consistency with previous studies within the program.

05 August 2020	Amendment 2, included the following non-administrative changes: • Added study and drug name and name of the new Clinical Study Director; references to "snOH" were changed to "symptomatic nOH" to clearly define disease under study and consistency throughout the document • Study design updated for the implementation of the Decentralized Platform in response to the COVID-19 pandemic • Clarification and elaboration that the number of participants in this study was based upon the number of participants completing Study 0170, and the anticipated incidence of syncopal and hypertensive events driven by this enrollment number • Re-ordered procedures for consistency with other ampreloxetine protocols 0169 and 0170 • Study 0145 was completed, and the results were presented in the protocol; clarified with more recent information regarding study status • Clarified where study visits could be conducted along with the inclusion of unscheduled visits • Introduced the Study Reference Manual as source • Additional instructions provided regarding the conduct of remote and in-clinic study visits and where reader could find additional details • Provided clarity on the optimal time(s) protocol procedures should be conducted • Removed statement regarding timing of ECG • Added information and instructions regarding the Unscheduled Visit • Maintaining a constant smoking habit was not required • Clarified that participants would be discontinued from the study in addition to stopping study medication if a stopping criterion was met • Contact information for medical monitoring was updated for coverage of Latin America sites • This was a safety study, and no efficacy data were analyzed • Introduction of statistical group providing support for IDMC • Updated principal investigator responsibility to include oversight of home health provider working with the site • Added additional information regarding electronic clinical outcome assessment data collection.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: