Clinical trial results:
External Natural History Controlled, open-Label Intervention Study to Assess the Efficacy and Safety of Long-Term Treatment with Raxone® in Leber's Hereditary Optic Neuropathy (LHON)

Summary

EudraCT number	2015-004405-16
Trial protocol	AT DE BE PT ES BG PL IT
Global end of trial date	29 March 2021

Results information

Result version number	v1 (current)
This version publication date	28 August 2022
First version publication date	28 August 2022

Trial information

Trial identification

Sponsor protocol code	SNT-IV-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02774005
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Santhera Pharmaceuticals (Switzerland) Ltd
Sponsor organisation address	Hohenrainstrasse 24, Pratteln, Switzerland, 4133
Public contact	Regulatory Affairs Manager, Santhera Pharmaceuticals (Switzerland) Ltd, 41 79 811 01 98, julien.gaudias@santhera.com
Scientific contact	Regulatory Affairs Manager, Santhera Pharmaceuticals (Switzerland) Ltd, 41 79 811 01 98, julien.gaudias@santhera.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	13 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 March 2021
Global end of trial reached?	Yes
Global end of trial date	29 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess efficacy of Raxone® in the promotion of recovery or stabilization of visual acuity in patients treated with Raxone® ≤1 year after the onset of symptoms, compared to an external natural history control group of idebenone naïve patients

Protection of trial subjects:

This study was conducted according to the guidelines of Good Clinical Practice (GCP), ICH E3 (CPMP/ICH/135/95), the US Code of Federal Regulations governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), Institutional Review Boards (21 CFR 56), Investigational New Drug Application (21 CFR 312), and Applications for FDA Approval to Market a New Drug (21 CFR 314), in compliance with the World Medical Assembly Declaration of Helsinki and its most recent amendments and applicable local regulatory requirements and laws

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2016
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: 39
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United Kingdom: 29
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	United States: 70
Worldwide total number of subjects	199
EEA total number of subjects	129

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)	29
Adults (18-64 years)	164
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

214 patients were assessed for eligibility. 15 patients were excluded because they did not meet the inclusions criteria. A total of 199 patients were enrolled in the study (198 received treatment and were included in the Safety Population). There were 196 patients in the ITT population.

Pre-assignment

Screening details:

214 patients were assessed for eligibility. 15 patients were excluded because they did not meet the inclusions criteria. A total of 199 patients were enrolled in the study (198 received treatment and were included in the Safety Population). There were 196 patients in the ITT population.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

not blinded

Arms

Arm title	Idebenone 300mg TiD

Arm description:

All patients received Raxone® study drug at the same dose; there was no randomization procedure. Patients received 900 mg Raxone® (2 tablets 3 times daily (TiD) with meals) for 24 months.

Arm type	Experimental
Investigational medicinal product name	Raxone
Investigational medicinal product code	
Other name	idebenone
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received 900 mg Raxone® (2 tablets 3 times daily with meals) for 24 months.

Number of subjects in period 1	Idebenone 300mg TiD
Started	199
Completed	138
Not completed	61
Adverse event, serious fatal	1
Pt unable to return for visits. Sent medicati	1
Consent withdrawn by subject	23
Due to Covid 19 lockdown V9 was not completed	1
Lack of compliance with study medication	4

cardiologist imposed travel restriction	1
Adverse event, non-fatal	8
Pt not willing to perform onsiteV9. didnt withdraw	1
Lost to follow-up	7
another study	1
subject is enrolling in a different LHON study tha	1
Genetic diagnosis reveals that a patient does not	12

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	199	199	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	29	29	
Adults (18-64 years)	164	164	
From 65-84 years	6	6	
85 years and over	0	0	
Age continuous			
Age continuous entry numbers are based on the Safety Population n=198.			
Units: years			
median	34.2		
standard deviation	± 15.2	-	
Gender categorical			
Gender categorical entry numbers are based on the safety Population n=198.			
Units: Subjects			
Female	53	53	
Male	146	146	

Subject analysis sets

Subject analysis set title	External natural history control group
Subject analysis set type	Per protocol

Subject analysis set description:

Natural History (NH) comparator group: Eligible subjects/eyes for matching (n=372 pts/731eyes), Natural History comparator Group matched to LEROS mITT used for Evaluation of 12months endpoints, NH matched N=106

Reporting group values	External natural history control group		
Number of subjects	106		
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)	372		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Age continuous entry numbers are based on the Safety Population n=198.			
Units: years			
median			
standard deviation	±		
Gender categorical			
Gender categorical entry numbers are based on the safety Population n=198.			
Units: Subjects			
Female	88		
Male	18		

End points

End points reporting groups

Reporting group title	Idebenone 300mg TiD

Reporting group description:

All patients received Raxone® study drug at the same dose; there was no randomization procedure. Patients received 900 mg Raxone® (2 tablets 3 times daily (TiD) with meals) for 24 months.

Subject analysis set title	External natural history control group
Subject analysis set type	Per protocol

Subject analysis set description:

Natural History (NH) comparator group: Eligible subjects/eyes for matching (n=372 pts/731eyes), Natural History comparator Group matched to LEROS mITT used for Evaluation of 12months endpoints, NH matched N=106

Primary: Proportion of eyes that achieved CRB at M12 in those pts that started treatment with Raxone ≤1 year after onset of symptoms, compared to eyes in matching external NH control group

End point title	Proportion of eyes that achieved CRB at M12 in those pts that started treatment with Raxone ≤1 year after onset of symptoms, compared to eyes in matching external NH control group

End point description:

PEP was the proportion of eyes that achieved a Clinically Relevant Benefit (CRB) (that is, in which there was either a Clinically Relevant Recovery [CRR] of VA from Baseline or a Clinically Relevant Stabilization [CRS]) at Month 12 in those patients that started treatment with Raxone® ≤1 year after the onset of symptoms, compared to eyes in the matching external NH control group.

End point type	Primary

End point timeframe:

at Month 12

End point values	Idebenone 300mg TiD	External natural history control group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	80[1]	106[2]		
Units: eyes				
number (not applicable)	60	40		

Notes:

[1] - Overall Number of Eyes Analyzed for PEP:142

[2] - Overall Number of Eyes Analyzed for PEP: 193
Natural history group matched to mITT LEROS: N=106

Statistical analyses

Statistical analysis title	primary endpoint
Comparison groups	Idebenone 300mg TiD v External natural history control group

Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021 [3]
Method	Wald-Chi-Squares

Notes:

[3] - P-values for Type 3 Tests are based on Wald Chi-Squares

Secondary: SEP1:Components of the primary endpoint: proportion of eyes with CRR of VA from Baseline at Month 12 compared to matching external NH control group

End point title	SEP1:Components of the primary endpoint: proportion of eyes with CRR of VA from Baseline at Month 12 compared to matching external NH control group

End point description:

End point type	Secondary

End point timeframe:

at Month 12

End point values	Idebenone 300mg TiD			
Subject group type	Reporting group			
Number of subjects analysed	80[4]			
Units: eyes				
number (not applicable)				
eyes with CRR	47			

Notes:

[4] - Overall Number of eyes Analyzed:142

Statistical analyses

No statistical analyses for this end point

Secondary: SEP2: Components of the primary endpoint: proportion of eyes in which Baseline VA better than 1.0 logMAR was maintained at Month 12 (CRS) compared to matching external NH control group

End point title	SEP2: Components of the primary endpoint: proportion of eyes in which Baseline VA better than 1.0 logMAR was maintained at Month 12 (CRS) compared to matching external NH control group

End point description:

End point type	Secondary

End point timeframe:

at Month 12

End point values	Idebenone 300mg TiD			
Subject group type	Reporting group			
Number of subjects analysed	22[5]			
Units: eyes				
number (not applicable)				
eyes with CRS	20			

Notes:

[5] - Overall Number of eyes Analyzed:31

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
>24 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24

Reporting groups	
Reporting group title	Raxone 300mg TiD

Reporting group description: -

Serious adverse events	Raxone 300mg TiD		
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 198 (13.64%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Disease Reoccurance			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
Miscarriage of partner			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	3 / 198 (1.52%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Alcohol abuse			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anxiety disorder			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychotic behaviour			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			

Alanine aminotransferase increased				
subjects affected / exposed	2 / 198 (1.01%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood creatine phosphokinase increased				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urobilinogen urine increased				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Ankle fracture				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thermal burn				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac arrest				

subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Dizziness				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple sclerosis				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Pancreatitis				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				

Hepatic failure				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Skin and subcutaneous tissue disorders				
Drug reaction with eosinophilia and systemic				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rash maculo-papular				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis intestinal perforated				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				

subjects affected / exposed	1 / 198 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Trichomoniasis			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vulvovaginitis			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Ketoacidosis			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Raxone 300mg TiD		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	148 / 198 (74.75%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	3 / 198 (1.52%)		
occurrences (all)	3		
Orthostatic hypotension			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Raynaud's phenomenon			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 198 (1.01%)		
occurrences (all)	2		
Chills			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Cyst			
subjects affected / exposed	2 / 198 (1.01%)		
occurrences (all)	3		
Fatigue			
subjects affected / exposed	8 / 198 (4.04%)		
occurrences (all)	8		
Influenza like illness			
subjects affected / exposed	4 / 198 (2.02%)		
occurrences (all)	5		

Malaise subjects affected / exposed occurrences (all)	5 / 198 (2.53%) 5		
Medical device pain subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 2		
Pain subjects affected / exposed occurrences (all)	4 / 198 (2.02%) 4		
Polyp subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	3 / 198 (1.52%) 6		
Social circumstances Orthosis user subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Reproductive system and breast disorders Cervical dysplasia subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Dysmenorrhoea subjects affected / exposed occurrences (all)	3 / 198 (1.52%) 9		
Testicular pain subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Upper-airway cough syndrome subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Respiratory, thoracic and mediastinal disorders Allergic bronchitis			

subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Asthma				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	10			
Cough				
subjects affected / exposed	12 / 198 (6.06%)			
occurrences (all)	14			
Dysphonia				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Dyspnoea				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Epistaxis				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Nasal congestion				
subjects affected / exposed	4 / 198 (2.02%)			
occurrences (all)	7			
Oropharyngeal pain				
subjects affected / exposed	14 / 198 (7.07%)			
occurrences (all)	22			
Pulmonary congestion				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Respiratory acidosis				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Sinus congestion				
subjects affected / exposed	2 / 198 (1.01%)			
occurrences (all)	2			
Tonsillar hypertrophy				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Upper respiratory tract congestion				

subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Psychiatric disorders			
Adjustment disorder with depressed mood			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Anger			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	4 / 198 (2.02%)		
occurrences (all)	4		
Confusional state			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Depressed mood			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	8 / 198 (4.04%)		
occurrences (all)	8		
Depressive symptom			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Hallucination			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Hallucination, visual			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Insomnia			

subjects affected / exposed	4 / 198 (2.02%)		
occurrences (all)	4		
Irritability			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Mood altered			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Mood swings			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Panic attack			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Restlessness			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	2 / 198 (1.01%)		
occurrences (all)	2		
Suicidal behaviour			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Suicidal ideation			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Glycosuria			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	15 / 198 (7.58%)		
occurrences (all)	16		
Aspartate aminotransferase increased			

subjects affected / exposed	13 / 198 (6.57%)			
occurrences (all)	13			
Bacterial test positive				
subjects affected / exposed	4 / 198 (2.02%)			
occurrences (all)	4			
Blood alkaline phosphatase increased				
subjects affected / exposed	3 / 198 (1.52%)			
occurrences (all)	3			
Blood bicarbonate decreased				
subjects affected / exposed	2 / 198 (1.01%)			
occurrences (all)	2			
Blood bilirubin increased				
subjects affected / exposed	3 / 198 (1.52%)			
occurrences (all)	4			
Blood cholesterol increased				
subjects affected / exposed	4 / 198 (2.02%)			
occurrences (all)	4			
Blood creatine phosphokinase				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Blood creatine phosphokinase increased				
subjects affected / exposed	14 / 198 (7.07%)			
occurrences (all)	15			
Blood creatinine increased				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Blood glucose increased				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Blood phosphorus decreased				
subjects affected / exposed	2 / 198 (1.01%)			
occurrences (all)	2			
Blood triglycerides increased				
subjects affected / exposed	5 / 198 (2.53%)			
occurrences (all)	6			

Blood urea decreased				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Blood urea increased				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Blood uric acid increased				
subjects affected / exposed	2 / 198 (1.01%)			
occurrences (all)	2			
Eosinophil count increased				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Gamma-glutamyltransferase increased				
subjects affected / exposed	9 / 198 (4.55%)			
occurrences (all)	9			
Gastric pH decreased				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Haematocrit decreased				
subjects affected / exposed	2 / 198 (1.01%)			
occurrences (all)	2			
Haemoglobin decreased				
subjects affected / exposed	2 / 198 (1.01%)			
occurrences (all)	2			
Liver function test increased				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Lymphocyte count decreased				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Lymphocyte count increased				
subjects affected / exposed	3 / 198 (1.52%)			
occurrences (all)	3			
Mean cell volume increased				

subjects affected / exposed	2 / 198 (1.01%)			
occurrences (all)	2			
Monocyte count decreased				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Monocyte count increased				
subjects affected / exposed	2 / 198 (1.01%)			
occurrences (all)	3			
Neutrophil count decreased				
subjects affected / exposed	4 / 198 (2.02%)			
occurrences (all)	4			
Neutrophil count increased				
subjects affected / exposed	3 / 198 (1.52%)			
occurrences (all)	3			
Protein urine present				
subjects affected / exposed	4 / 198 (2.02%)			
occurrences (all)	5			
Red blood cell count decreased				
subjects affected / exposed	2 / 198 (1.01%)			
occurrences (all)	2			
Transaminases increased				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Urinary sediment present				
subjects affected / exposed	2 / 198 (1.01%)			
occurrences (all)	2			
Urine ketone body present				
subjects affected / exposed	2 / 198 (1.01%)			
occurrences (all)	2			
Weight increased				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
White blood cell count decreased				
subjects affected / exposed	3 / 198 (1.52%)			
occurrences (all)	3			
White blood cell count increased				

subjects affected / exposed	3 / 198 (1.52%)		
occurrences (all)	3		
White blood cells urine positive			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Arthropod sting			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	2		
Contusion			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	2		
Corneal abrasion			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Foot fracture			
subjects affected / exposed	2 / 198 (1.01%)		
occurrences (all)	2		
Foreign body in eye			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	2		
Head injury			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Heat stroke			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Lower limb fracture			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Overdose			

subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Product administration error subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Radius fracture subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Skin laceration subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Sunburn subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Tendon rupture subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Thermal burn subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Wound subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Congenital, familial and genetic disorders			
Hereditary optic atrophy subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Cardiac disorders			
Coronary artery disease subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Tachycardia subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Nervous system disorders			

Burning sensation				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Dizziness				
subjects affected / exposed	4 / 198 (2.02%)			
occurrences (all)	5			
Generalised tonic-clonic seizure				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Headache				
subjects affected / exposed	37 / 198 (18.69%)			
occurrences (all)	131			
Hyperaesthesia				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Migraine				
subjects affected / exposed	2 / 198 (1.01%)			
occurrences (all)	2			
Ophthalmic migraine				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	2			
Presyncope				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Seizure				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Sinus headache				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Somnolence				
subjects affected / exposed	4 / 198 (2.02%)			
occurrences (all)	4			
Syncope				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			

Tremor subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Splenomegaly subjects affected / exposed occurrences (all)	 2 / 198 (1.01%) 2 1 / 198 (0.51%) 1		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) Excessive cerumen production subjects affected / exposed occurrences (all) Hypoacusis subjects affected / exposed occurrences (all) Motion sickness subjects affected / exposed occurrences (all)	 3 / 198 (1.52%) 3 1 / 198 (0.51%) 1 1 / 198 (0.51%) 1 1 / 198 (0.51%) 1		
Eye disorders Blepharitis subjects affected / exposed occurrences (all) Eye haemorrhage subjects affected / exposed occurrences (all) Eye pain subjects affected / exposed occurrences (all) Eyelid pain subjects affected / exposed occurrences (all) Lacrimation increased	 1 / 198 (0.51%) 1 1 / 198 (0.51%) 1 5 / 198 (2.53%) 5 1 / 198 (0.51%) 1		

subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Ocular hyperaemia			
subjects affected / exposed	2 / 198 (1.01%)		
occurrences (all)	2		
Photophobia			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Photopsia			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Pupils unequal			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	2 / 198 (1.01%)		
occurrences (all)	2		
Visual acuity reduced			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Visual impairment			
subjects affected / exposed	5 / 198 (2.53%)		
occurrences (all)	5		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	3 / 198 (1.52%)		
occurrences (all)	4		
Abdominal migraine			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	8 / 198 (4.04%)		
occurrences (all)	10		
Abdominal pain upper			
subjects affected / exposed	13 / 198 (6.57%)		
occurrences (all)	14		

Constipation				
subjects affected / exposed	2 / 198 (1.01%)			
occurrences (all)	2			
Dental caries				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Dental necrosis				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Diarrhoea				
subjects affected / exposed	19 / 198 (9.60%)			
occurrences (all)	28			
Dyspepsia				
subjects affected / exposed	5 / 198 (2.53%)			
occurrences (all)	9			
Eosinophilic oesophagitis				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Food poisoning				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Frequent bowel movements				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Gastritis				
subjects affected / exposed	2 / 198 (1.01%)			
occurrences (all)	10			
Gastrointestinal pain				
subjects affected / exposed	2 / 198 (1.01%)			
occurrences (all)	2			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Infrequent bowel movements				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			

Malpositioned teeth subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 2		
Nausea subjects affected / exposed occurrences (all)	15 / 198 (7.58%) 20		
Salivary hypersecretion subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Tooth disorder subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Tooth impacted subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Toothache subjects affected / exposed occurrences (all)	7 / 198 (3.54%) 14		
Vomiting subjects affected / exposed occurrences (all)	6 / 198 (3.03%) 7		
Pyrexia subjects affected / exposed occurrences (all)	5 / 198 (2.53%) 6		
Hepatobiliary disorders Hepatosplenomegaly subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Hypersensitivity subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Skin and subcutaneous tissue disorders Pregnancy of partner subjects affected / exposed occurrences (all)	2 / 198 (1.01%) 2		
Acne			

subjects affected / exposed	2 / 198 (1.01%)		
occurrences (all)	3		
Alopecia			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Ingrown hair			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Psoriasis			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	6 / 198 (3.03%)		
occurrences (all)	7		
Rash pruritic			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Scab			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Skin fissures			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Skin irritation			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Skin lesion			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	3 / 198 (1.52%)		
occurrences (all)	6		

Haematuria			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Nephrolithiasis			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Urine abnormality			
subjects affected / exposed	3 / 198 (1.52%)		
occurrences (all)	3		
Prostatitis			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Thyroiditis			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 198 (1.52%)		
occurrences (all)	4		
Arthritis			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	9 / 198 (4.55%)		
occurrences (all)	13		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	2 / 198 (1.01%)		
occurrences (all)	2		
Musculoskeletal discomfort			

subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	3 / 198 (1.52%)		
occurrences (all)	5		
Neck pain			
subjects affected / exposed	3 / 198 (1.52%)		
occurrences (all)	3		
Osteoporosis			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	2 / 198 (1.01%)		
occurrences (all)	2		
Pain in jaw			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Periarthritis			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Synovial cyst			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Tendonitis			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Infections and infestations			
Bacterial abdominal infection			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Bacteriuria			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	4 / 198 (2.02%)		
occurrences (all)	6		

Bronchitis viral				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Candida infection				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Cellulitis				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Conjunctivitis				
subjects affected / exposed	2 / 198 (1.01%)			
occurrences (all)	2			
Ear infection				
subjects affected / exposed	2 / 198 (1.01%)			
occurrences (all)	2			
Enterobiasis				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Eye infection				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Fungal skin infection				
subjects affected / exposed	2 / 198 (1.01%)			
occurrences (all)	2			
Gastroenteritis				
subjects affected / exposed	4 / 198 (2.02%)			
occurrences (all)	5			
Gastroenteritis viral				
subjects affected / exposed	3 / 198 (1.52%)			
occurrences (all)	3			
Gastrointestinal viral infection				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Hepatitis C				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			

Herpes zoster				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Hordeolum				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Infection				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Influenza				
subjects affected / exposed	8 / 198 (4.04%)			
occurrences (all)	9			
Lower respiratory tract infection				
subjects affected / exposed	3 / 198 (1.52%)			
occurrences (all)	5			
Nasopharyngitis				
subjects affected / exposed	33 / 198 (16.67%)			
occurrences (all)	51			
Oral herpes				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Pharyngitis streptococcal				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Pulpitis dental				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Rhinitis				
subjects affected / exposed	1 / 198 (0.51%)			
occurrences (all)	1			
Sinusitis				
subjects affected / exposed	7 / 198 (3.54%)			
occurrences (all)	8			

Skin infection subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1			
Tooth abscess subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1			
Tooth infection subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 2			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 198 (2.53%) 7			
Urinary tract infection subjects affected / exposed occurrences (all)	4 / 198 (2.02%) 5			
Viral infection subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1			
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1			
Dehydration subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1			
Fluid retention subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1			
Hypercholesterolaemia subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1			
Hyperlipidaemia subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1			
Hypertriglyceridaemia				

subjects affected / exposed	3 / 198 (1.52%)		
occurrences (all)	4		
Hyponatraemia			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Periostitis			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2017	Amendment 1: 1.Amendment to the Study Administrative Structure to update the study team details after changes at Santhera. 2. Amendment to the Synopsis and Section 3.1 to reflect plans to expand the study to the Rest of the World. 3. Amendment to the Synopsis, Sections 6 and 6.5.1 to clarify that only patients that do not have a known LHON-specific DNA mutation will be withdrawn from the study. 4. Amendment to Section 1.1 to update the percentage of individuals with LHON that harbor one of three point mutations in mitochondrial DNA to more than 90%. 5. Amendment to Synopsis, Study flow chart, Sections 6.2, 6.2.1, 8.5.1 and 8.6.1 to update study assessment instructions. 6. Amendment to Section 8.2.2 to state where reference safety information can be found. 7. Addition of Section 8.2.5 to describe the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) by the Sponsor. 8. Amendment to Section 10.15 to clarify under which circumstances access to study drug would be possible after a patient completes
06 March 2019	Amendment 2: 1. Amendment to the Study Administrative Structure to update Santhera study team changes and change of the CRO name. 2. Amendment to the Signature page after change in protocol signature process and changes in the study team. 3. Amendment to Sections 4.4 and 11 to clarify that the reference guideline on contraception for this trial is the Clinical Trial Facilitation Group Guidance on Contraception 2014. 4. Amendment to Section 6.3.2 to update information on interaction with other medicinal products. 5. Amendment to Section 8.1.2 to add guidance on the definition and reporting of Adverse Events of Special Interest (AESI). 6. Amendment to Sections 8.1.6 and 8.2.3 to clarify the definition of related/unrelated AE and SAEs. 7. Amendment to Section 9.3.1 to better define the Intent-To-Treat population. 8. Amendment to Section 9.5 and the synopsis to update timelines on the preparation of the statistical analysis plan. 9. Amendment to Section 3.1, 3.2 and 9.6 and synopsis to update the number of patients to be enrolled to the LEROS study based on sample size re-calculation. 10. Amendment to Section 10.1 to clarify the notification of Urgent Safety Measures by the Investigator to the Sponsor and IRB/IEC. 11. Amendment to Section 10.4 to clarify that Quality Risk Assessment for the trial will be performed according to Santhera SOPs. 12. Amendment to Section 10 to add Section 10.18 referring to the registration of the Clinical Trial in a Publicly Accessible Database. 13. Minor editorial changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported