



## 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
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##### 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:

<b>Subjects enrolled per age group</b>	
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
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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 <sup>[1]</sup>	106 <sup>[2]</sup>		
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 <sup>[3]</sup>
Method	Wald-Chi-Squares

Notes:

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

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**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**

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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
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End point description:

End point type	Secondary
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End point timeframe:

at Month 12

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

Notes:

[4] - Overall Number of eyes Analyzed:142

**Statistical analyses**

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No statistical analyses for this end point

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**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**

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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
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End point description:

End point type	Secondary
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End point timeframe:

at Month 12

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<b>End point values</b>	Idebenone 300mg TiD			
Subject group type	Reporting group			
Number of subjects analysed	22 <sup>[5]</sup>			
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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24
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### Reporting groups

Reporting group title	Raxone 300mg TiD
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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 Reoccurrence			
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 %



<b>Non-serious adverse events</b>	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	1 / 198 (0.51%)		
occurrences (all)	1		
Product administration error			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Radius fracture			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Skin laceration			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Sunburn			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Tendon rupture			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Thermal burn			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Hereditary optic atrophy			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	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 occurrences (all)	1 / 198 (0.51%) 1		
Nephrolithiasis subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Urine abnormality subjects affected / exposed occurrences (all)	3 / 198 (1.52%) 3		
Prostatitis subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Thyroiditis subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	3 / 198 (1.52%) 4		
Arthritis subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Back pain subjects affected / exposed occurrences (all)	9 / 198 (4.55%) 13		
Intervertebral disc protrusion subjects affected / exposed occurrences (all)	1 / 198 (0.51%) 1		
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	2 / 198 (1.01%) 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	1 / 198 (0.51%)		
occurrences (all)	1		
Tooth abscess			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	5 / 198 (2.53%)		
occurrences (all)	7		
Urinary tract infection			
subjects affected / exposed	4 / 198 (2.02%)		
occurrences (all)	5		
Viral infection			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Dehydration			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Fluid retention			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Hypercholesterolaemia			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	1		
Hyperlipidaemia			
subjects affected / exposed	1 / 198 (0.51%)		
occurrences (all)	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

