CLINICAL TRIAL PROTOCOL

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

(LEROS)

Open-Label Study to assess the Efficacy and Safety of Idebenone in LHON Patients

Compound:	idebenone
Phase:	III (US)/ IV (EU)
Protocol Number:	SNT-IV-005
Version:	2.1_US
Date:	6 March 2019
Study Acronym:	LEROS
EudraCT Number:	2015-004405-16
US IND Number:	107,390

Property of Santhera Pharmaceuticals (Switzerland) Limited

Study Administrative Structure

Name:	Santhera Pharmaceuticals (Switzerland) Limited
Responsibility:	Sponsor
Address:	Hohenrainstrasse 24 4133 Pratteln, Switzerland
Phone:	+41 61 906 89 50
Fax:	+41 61 906 89 51

Name:	Antonio Perez, MD
Responsibility:	Clinical Research Physician
Address	Santhera Pharmaceuticals (Switzerland) Ltd
Phone:	+41 79 602 8998
Fax:	+41 61 906 8951
e-mail:	toni.perez@santhera.com

Name:	Andrea Elischer
Responsibility:	Clinical Trial Leader
Address:	Santhera Pharmaceuticals (Switzerland) Ltd
Phone:	+41 61 906 89 07
e-mail:	andrea.elischer@santhera.com

Name:	Omer De Mol
Responsibility:	Head of Drug Safety and Pharmacovigilance
Address:	Santhera Pharmaceuticals (Switzerland) Ltd
Phone:	+41 61 906 8904
Fax:	+41 61 906 8951
e-mail:	Omer.deMol@santhera.com

Name:	IQVIA (previously called Quintiles IMS)
Responsibility:	Monitoring, data management, Statistics
Address:	500 Brook Drive Green Park Reading, Berkshire, RG2 6UU, United Kingdom

Notification in case of Serious Adverse Events and Adverse Events of Special Interest (AESI):

Name:	United BioSource Corporation EU Safety Services
Address:	16, Chemin des Coquelicots CH-1214 Vernier/Geneva, Switzerland
Phone:	+41 22 596 44 44
Fax:	+41 22 596 44 46
e-mail:	EUSafety@ubc.com

Investigators / Investigational Sites:

This is a multinational study that includes U.S sites operating under the IND and foreign sites not under the IND.

Principal investigator (IND site)

Name:	Dr. Marc. H. Levin, MD, PhD
Address:	Department of Ophthalmology Palo Alto Medical Foundation 301 Industrial Road, Fourth Floor San Carlos, CA 94070
Phone:	+1-650-596-4220
Fax:	+1-650-508-8540
e-mail:	levinmh@pamf.org

Principal investigator (Non-IND site)

Name:	Prof. Dr. med. Thomas Klopstock
Address:	Friedrich-Baur-Institut an der Neurologischen Klinik Klinikum der Universität München - Innenstadt Ziemssenstr. 1; 80336 München; Germany
Phone:	+49-89-4400-57474
Fax:	+49-89-4400-57402
e-mail:	tklopsto@med.lmu.de

For further investigators / Investigational sites: See separate listing.

CLINICAL TRIAL PROTOCOL
Version 2.1

Signature Page

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

SNT-IV-005

(LEROS)
Open-Label Study to assess the Efficacy and Safety of Idebenone in LHON Patients

The study will be conducted according to the protocol, the latest version of the Declaration of Helsinki, with the current requirements for Good Clinical Practice (ICH-E6; CPMP/ICH/135/95) and with local laws and regulations.

This protocol has been verified and approved by:

Sponsor

..... **Date:** 15 APR 2019

Antonio Perez , MD
Santhera Pharmaceuticals (Switzerland) Ltd
Hohenrainstrasse 24
4133 Pratteln
Switzerland
Phone +41 79 602 89 98
Fax: +41 61 906 89 51

Synopsis

Study Title	External Natural History Controlled, open-Label Intervention Study to Assess the Efficacy and Safety of Long-Term Treatment with idebenone in Leber's Hereditary Optic Neuropathy (LHON)
Study Number	SNT-IV-005
Study Phase	III (US)/ IV (EU)
Study Acronym	LEROS
Planned Study Duration	Up to 49 months including 24 months for recruitment, 24 months of treatment and 1 month for follow up visit
Investigational Product Dosage and Route of Administration	Idebenone 150 mg tablets (Raxone® is the branded name in the EU) 900 mg/day (2 x 150 mg to be taken orally 3 times daily with meals)
Control Group	Natural history visual acuity outcomes in idebenone naïve patients collected as case record survey will be used as an external control group
Indication	Leber's Hereditary Optic Neuropathy (LHON)
Study Objectives	**Primary Objective:** • To assess efficacy of idebenone in the promotion of recovery or stabilization of visual acuity (VA) in patients treated with idebenone ≤1 year after the onset of symptoms, compared to an external natural history control group of idebenone naïve patients **Secondary Objectives:** • To assess efficacy of idebenone in the promotion of recovery or stabilization of visual acuity in LHON patients treated with >1 year after the onset of symptoms, compared to an external natural history control group of idebenone naïve patients • To compare the promotion of recovery or stabilization of visual acuity in LHON patients treated with idebenone ≤1 and >1 year after the onset of symptoms • To assess the influence of mutation on the promotion of recovery or stabilization of visual acuity in LHON patients treated with idebenone • To assess the influence of time since onset of symptoms prior to the initiation of treatment with idebenone on the promotion of recovery or stabilization of visual acuity in LHON patients • To assess the influence of duration of treatment with idebenone on changes in visual acuity in LHON patients • To assess safety of long-term treatment of LHON patients with idebenone
Study Endpoints	**Primary Endpoint:** • Proportion of eyes with clinically relevant recovery of visual acuity from Baseline or in which Baseline VA better than 1.0 logMAR was maintained at Month 12 in patients treated with idebenone ≤1 year after the onset of symptoms, compared to matching external natural history control group Clinically Relevant Recovery (CRR) is defined as a change from "off-chart" visual acuity to at least 1.6 logMAR value or an improvement of at least 0.2 logMAR value within "on-chart". **Secondary Endpoints:**

- Components of the primary endpoint:
  - Proportion of eyes with CRR of VA from Baseline at Month 12 compared to matching external natural history control group
  - Proportion of eyes in which Baseline VA better than 1.0 logMAR was maintained at Month 12 compared to matching external natural history control group
- Proportion of eyes in patients treated with idebenone >1 year after the onset of symptoms with CRR of VA from Baseline or in which Baseline VA better than 1.0 logMAR was maintained at Month 12 compared to the external natural history control group, in all patients and classified by mutation
- Proportion of eyes and patients treated with idebenone ≤1 year after the onset of symptoms with CRR of VA from Baseline or in which Baseline visual acuity better than 1.0 logMAR was maintained following 6, 18 and 24 months of treatment with idebenone compared to matching external natural history control group, in all patients and classified by mutation
- Proportion of eyes/patients treated with idebenone ≤1 year or >1 year after the onset of symptoms with "Off-chart" VA at Baseline in whom VA improves to better than 1.60 logMAR by Month 6, 12, 18 and 24
- Proportion of eyes/patients treated with idebenone ≤1 year or >1 year after the onset of symptoms with VA in the categories of better than 1.0 logMAR, 1.0 to 1.68 logMAR and above 1.68 logMAR at each assessment time point up to Month 24
- Safety as assessed by AE count and laboratory analyses during the study

Background and Rationale

The randomized, placebo-controlled RHODOS (SNT-II-003) trial (Klopstock et al., 2011), the retrospective cohort study of Carelli et al., (2011), Santhera's ongoing Expanded Access Program (EAP) and several case reports (summarized in Gueven and Faldu, 2013), provide evidence that idebenone promotes the recovery of VA in patients with LHON. However, due to the nature of these datasets, this evidence is not considered comprehensive. In view of the urgent medical need and poor prognosis of LHON if untreated, a randomized, placebo-controlled study to provide comprehensive data is not considered feasible in LHON. An open-label study is therefore considered the most appropriate strategy for gathering additional evidence for the efficacy of idebenone in the treatment of LHON. The primary objective of this study is therefore to compare the outcomes for patients treated with Idebenone in this study with those of matching untreated patients from an external natural history control group generated in a historical case record survey (CRS).

In RHODOS, LHON patients enrolling up to 5 years after the onset of symptoms of disease were treated with idebenone. Whilst natural history VA outcomes data collected from LHON patients early in the course of the disease is available, relatively little reliable natural history VA outcomes data is available from patients with longer disease durations. The primary endpoint of this study will therefore compare the VA outcomes for patients treated with idebenone ≤1 year of the onset of symptoms with matching natural history control data. Secondary endpoints will include outcomes for patients treated with idebenone >1 year after the onset of symptoms. Since LHON is known to lead to the apoptotic loss of retinal ganglion cells where the extent of loss increases with time since onset of disease, this study will explore further the relationship between time since onset at the initiation of

	idebenone therapy and CRR, where possible compared to untreated control patients. The treatment duration in RHODOS was 6 months and a larger proportion of idebenone-treated patients presented with CRR in VA compared to placebo. However, data from Santhera's ongoing Expanded Access Program (EAP) indicates that prolonged treatment can increase both the proportions of patients with CRR of VA and the magnitude of the recovery observed. Furthermore, data from the RHODOS and from the EAP provide evidence that the LHON-causative mutation harboured is prognostic of CRR in VA. Therefore, secondary objectives of this study are to provide information on the effect of treatment duration on both the proportions of patients presenting with CRR and on the magnitude of any response with increasing treatment time and on the influence of the mutation harboured on CRR rate compared to spontaneous CRR (sCRR) in untreated control patients. The study will also allow the assessment of the safety and tolerability of long-term treatment with idebenone, with particular emphasis on the proportion of patients experiencing elevated Liver Function Tests (LFTs) or changes in blood cell counts.
Number of Centres	Approximately 35 Multinational study with US sites operating under IND and EU sites not operating under IND.
Number of Patients	80 patients presenting ≤1 year after the onset of symptoms will be enrolled to ensure 61 provide VA assessments following 12 months of idebenone treatment (primary endpoint). 80 patients presenting >1 year after the onset of symptoms will be enrolled to ensure 61 provide VA assessments following 12 months of idebenone treatment (secondary endpoint). Patients will be stratified according to time since onset of symptoms with a maximum of 30 patients to be enrolled in any of the strata of >1 - ≤2 years, >2 - ≤3 years, >3 - ≤4 years and >4 - ≤5 years since onset of symptoms.
Inclusion Criteria	1. Impaired visual acuity in affected eyes due to LHON 2. No explanation for visual loss besides LHON 3. Age ≥ 12 years 4. Onset of symptoms ≤5 years prior to Baseline 5. Confirmation of either G11778A, G3460A or T14484C LHON mtDNA (for the ITT population, not required for enrolment) 6. Written informed consent obtained from the patient 7. Ability and willingness to comply with study procedures and visits 8. Women of Childbearing Potential (WCBP) who have a negative urine or serum pregnancy test at Baseline visit and who are willing to use a highly effective contraceptive measure and maintain it until treatment discontinuation.
Exclusion Criteria	1. Patient has provided natural history data to the Case Record Survey (SNT-CRS-002) 2. Any previous use of idebenone 3. Any other cause visual impairment (e.g. glaucoma, diabetic retinopathy, AIDS related visual impairment, cataract, macular degeneration, etc.) or any active ocular disorder (uveitis, infections, inflammatory retinal disease, thyroid eye disease, etc.)

	4. Known history of clinically significant elevations (greater than 3 times the upper limit of normal) of AST, ALT or creatinine 5. Patient has a condition or is in a situation which, in an investigator's opinion may put the patient at significant risk, may confound study results or may interfere significantly with the patient's participation in the study 6. Participation in another clinical trial of any investigational drug within 3 months prior to Baseline 7. Hypersensitivity to the active substance or to any of the following excipients: Lactose monohydrate, Microcrystalline cellulose, Croscarmellose sodium, Povidone K25, Magnesium stearate, Colloidal silica, Macrogol 3350, Poly(vinyl alcohol), Talc, Titanium dioxide, Sunset yellow FCF (E110). 8. Women who are pregnant or have a positive pregnancy test at Baseline visit 9. Women who are breastfeeding.
Treatment Period	24 months
Study Design	Multicenter, interventional, open label study with external historical control group
Efficacy Assessments	Efficacy will be assessed at every visit by performing a VA test (logMAR).
Safety Evaluations	Safety will be assessed at every visit by evaluation of adverse events, and clinical laboratory evaluation of hematological and biochemical parameters (blood and urine samples).
Study Procedures	The study will be described to potentially eligible patients and Informed Consent will be obtained from the patient and/or parents/legal guardian prior to any study specific procedures being undertaken. There will be no screening visit for this study. Potential study participants will be assessed for eligibility of enrolment at Visit 1/Baseline. At **Visit 1/Baseline:** patient is informed about the trial and its procedures. Patient signs informed consent. Should the patient require additional time to consider participation in the trial, then a second Visit1/Baseline visit might be arranged. Study specific procedures will only be performed after the patient has signed the informed consent. The demographic characteristics will be collected. The medical history will be assessed and LHON diagnosis confirmed. Patients meeting inclusion/exclusion criteria and having signed the informed consent will be enrolled in the study. Enrolment failures and reasons thereof will be recorded in the CRF. In the absence of a genetic confirmation of the LHON mtDNA mutation, a blood sample will be taken for genetic testing. Should the genetic diagnosis reveal that a patient does not harbour a LHON-specific mtDNA mutation, the patient will be withdrawn from the study. It should be noted however that the VA outcomes for patients carrying one of the three major LHON-specific mtDNA mutations (G3460A, G11778A or T14484A) will be used in the primary analyses. Physical examination including height and weight, vital signs, and fundoscopic exam and visual acuity tests will be performed. Blood and urine samples and concomitant medication will be recorded.

Urine or serum pregnancy test will be taken for WCBP.

The investigator will dispense a patient diary and sufficient study medication to last until the next visit and instruct the patients carefully in their use.

Results from blood and urine test must be available before the patient starts taking study medication. The patient will be informed by the investigator or study nurse by phone should these results not be available at the day of Visit 1/Baseline.

The patient will take the first dose of study medication on Day 1 or the day the patient is informed to start study medication intake, whichever is applicable. The data of first dose of study medication intake is to be recorded in the patient diary.

The study subject will continue the daily recordings in the patient diary to be completed throughout the entire study period.

At **Visit 2/Month 1:** VA test will be performed. Blood and urine samples will be taken and the patient diary will be reviewed to assess the compliance, adverse events and concomitant medication.

A urine or serum pregnancy test will be performed for WCBP when clinically indicated.

The investigator will dispense a new patient diary and sufficient study medication to last until the next visit.

At Visit 3/Month 3: VA test will be performed. Blood and urine samples will be taken and the patient diary will be reviewed to assess the compliance, adverse events and concomitant medication.

A urine or serum pregnancy test will be performed for WCBP when clinically indicated.

The investigator will dispense a new patient diary and sufficient study medication to last until the next visit.

At **Visit 4/Month 6:** physical examination, vital signs and visual acuity tests will be performed. Blood and urine samples will be taken. The patient diary will be reviewed to assess the compliance, adverse events and concomitant medication.

A urine or serum pregnancy test will be performed for WCBP when clinically indicated.

The investigator will dispense a new patient diary and sufficient study medication to last until the next visit.

At **Visit 5/Month 9:** visual acuity test will be performed. Blood and urine samples will be taken and the patient diary will be reviewed to assess the compliance, adverse events and concomitant medication.

A urine or serum pregnancy test will be performed for WCBP when clinically indicated.

The investigator will dispense a new patient diary and sufficient study medication to last until the next visit.

At **Visit 6/Month 12:** physical examination, vital signs, fundoscopic exam and visual acuity tests will be performed. Blood and urine samples will be taken.

A urine or serum pregnancy test will be performed for WCBP when clinically indicated.

The investigator will dispense a new patient diary and sufficient study medication to last until the next visit.

At **Visit 7/Month 18:** physical examination, vital signs and visual acuity tests will be performed. Blood and urine samples will be taken and the patient diary will be reviewed to assess the compliance, adverse events and concomitant medication.

A urine or serum pregnancy test will be performed for WCBP when clinically indicated.

The investigator will dispense a new patient diary and sufficient study medication to last until the next visit.

At **Visit 8/Month 24:** physical examination, vital signs, fundoscopic exam and visual acuity tests will be performed. Blood and urine samples will be taken.

A urine or serum pregnancy test will be performed for WCBP when clinically indicated.

The investigator will dispense a new patient diary. No further study medication will be dispensed.

At **Visit 9**, 28-35 days after drug discontinuation, a visual acuity test will be performed. Blood and urine samples will be taken and the patient diary will be collected and reviewed to assess adverse events and concomitant medication. A fundoscopic exam may be performed if abnormalities were observed at the previous visit.

The patient will be informed that he/she completed the study.

Statistical Methods

Analysis Methods:

The VA outcomes for patients treated with idebenone ≤1 year after onset of symptoms will be compared to a matching external untreated natural history control group. The primary endpoint will be analysed using a logistic regression model. The binary response will be used as the dependent variable. The independent variables include the treatment group (idebenone treated patients versus untreated control group) and mutation (G11778A, G3460A, T14484C). All patients who have at least one post-baseline assessment at 12±3 months after Baseline will be included in the primary analysis. A sensitivity analysis assessing the impact of incomplete data will be performed with a generalized linear mixed model.

The VA outcomes for patients treated with idebenone >1 year after onset of symptoms will be compared to the natural history outcomes from untreated external control patients and to the VA outcomes for patients treated with idebenone ≤1 year after onset of symptoms.

Safety data will be analysed using descriptive statistics.

A detailed description of the statistical analysis methods will be provided in the Statistical Analysis Plan which will be finalized before database lock.

Study Flow Chart

Visits/Contacts:

Visit 1 / Baseline Day 1	• Informed Consent • Medical History and confirmation of LHON • Demographic characteristics • Confirmation of Inclusion/Exclusion criteria • Trial enrolment • Confirmation of LHON mtDNA mutation (or blood sample for genetic test) • Physical Examination (including height and weight) • Vital Signs • Fundoscopic Exam • Visual Acuity (logMAR) • Safety Blood and Urine samples • Urine or serum pregnancy test for WCBP • Concomitant Medication • Distribution of Study Medication • Distribution of Patient Diary
Visit 2 / Month 1 (± 1 week)	• Visual Acuity (logMAR) • Safety Blood and Urine samples • Urine or serum pregnancy test for WCBP when clinically indicated. • Assessment of Adverse Events • Concomitant Medication • Patient Compliance • Collection and Distribution of Patient Diary • Collection and Distribution of Study Medication
Visit 3 / Month 3 (± 1 week)	• Visual Acuity (logMAR) • Safety Blood and Urine samples • Urine or serum pregnancy test for WCBP when clinically indicated. • Assessment of Adverse Events • Concomitant Medication • Patient Compliance • Collection and Distribution of Patient Diary • Collection and Distribution of Study Medication
Visit 4 / Month 6 (± 1 week)	• Physical Examination • Vital Signs • Visual Acuity (logMAR) • Safety Blood and Urine samples • Urine or serum pregnancy test for WCBP when clinically indicated. • Assessment of Adverse Events • Concomitant Medication • Patient Compliance • Collection and Distribution of Patient Diary • Collection and Distribution of Study Medication

Visit 5 / Month 9 (± 1 week)	• Visual Acuity (logMAR) • Safety Blood and Urine samples • Urine or serum pregnancy test for WCBP when clinically indicated. • Assessment of Adverse Events • Concomitant Medication • Patient Compliance • Collection and Distribution of Patient Diary • Collection and Distribution of Study Medication
Visit 6 / Month 12 (± 1 week)	• Physical Examination • Vital Signs • Fundoscopic Exam • Visual Acuity (logMAR) • Safety Blood and Urine samples • Urine or serum pregnancy test for WCBP when clinically indicated. • Assessment of Adverse Events • Concomitant Medication • Patient Compliance • Collection and Distribution of Patient Diary • Collection and Distribution of Study Medication
Visit 7 / Month 18 (± 1 week)	• Physical Examination • Vital Signs • Visual Acuity (logMAR) • Safety Blood and Urine samples • Urine or serum pregnancy test for WCBP when clinically indicated. • Assessment of Adverse Events • Concomitant Medication • Patient Compliance • Collection and Distribution of Patient Diary • Collection and Distribution of Study Medication
Visit 8 / Month 24 (± 1 week)	• Physical Examination • Vital Signs • Fundoscopic Exam • Visual Acuity (logMAR) • Safety Blood and Urine samples • Urine or serum pregnancy test for WCBP when clinically indicated. • Assessment of Adverse Events • Concomitant Medication • Patient Compliance • Collection and Distribution of Patient Diary • Collection of Study Medication
Visit 9 / Follow Up Visit (28-35 Days after drug discontinuation)	• Fundoscopic Exam (Optional) • Visual Acuity (logMAR) • Safety Blood and Urine samples • Assessment of Adverse Events • Concomitant Medication • Collection of Patient Diary

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Amendment History

Amendment 1 (6 March 2019

1. Amendment to Study Administrative Structure to update study team after changes at Santhera and change of CRO name.

2. Amendment to Signature page after change in protocol signature process and changes in the study team.

3. Amendment to section 1.1 and section 11 to update percentage of individuals with LHON that harbour one of three point mutations in mitochondrial DNA to more than 90%.

4. Amendment to section 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.

5. Amendment to section 6.2 to correct an inconsistency in the footnote.

6. Amendment to section 6.3.2 to update information on interaction with other medicinal products.

7. Amendment to section 8.1.2 to add guidance on the definition and reporting of Adverse Events of Special Interest (AESI).

8. Amendment to section 8.1.6 and 8.2.3 to clarify the definition of related/unrelated AE and SAEs.

9. Amendment to section 9.3.1 to better define the Intent-To-Treat population.

10. Amendment to section 9.5 and synopsis to update timelines on the preparation of the statistical analysis plan.

11. 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.

12. Amendment to section 10.1 to clarify the notification of Urgent Safety Measures by the Investigator to the Sponsor and IRB/IEC.

13. Amendment to section 10.4 to clarify that Quality Risk Assessment for the trial will be performed according to Santhera SOPs.

14. Amendment to section 10 to add section 10.18 referring to the registration of the Clinical Trial in a Publicly Accessible Database.

15. Minor editorial changes.

List of Abbreviations

AE(s)	Adverse Event(s)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CF	Counting Fingers
CFR	Code of Federal Regulations
CHMP	Committee on Human Medicinal Products
CK	Creatine Kinase
CRF	Case Report Form
CRR	Clinically relevant recovery (of visual acuity)
CRS	Case Record Survey
DoB	Date of Birth
DSMB	Data Safety Monitoring Board
EAP	Expanded Access Program
EDC	Electronic Data Capture
GCP	Good Clinical Practices
GGT	Gamma-Glutamyl Transferase
HM	Hand Motion
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC/IRB	Independent Ethics Committee/Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LFT	Liver Function Test
LHON	Leber's Hereditary Optic Neuropathy
logMAR	Logarithm of the Minimum Angle of Resolution
LP	Light Perception
mtDNA	Mitochondrial Deoxyribonucleic acid
MMRM	Mixed Model for Repeated Measures
OLS	Open Label Study
PP	Per-Protocol
ROS	Reactive Oxygen Species
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
sCRR	Spontaneous Clinically Relevant Recovery
VA	Visual Acuity
WCBP	Women of Childbearing Potential

1 Introduction

1.1 Background

Leber's Hereditary Optic Neuropathy

LHON is a maternally inherited loss of vision due to atrophy of the optic nerve. More than 90% of individuals with LHON harbour one of three point mutations in mitochondrial DNA (mtDNA) (G11778A, T14484C, G3460A) affecting genes encoding complex I subunits of the respiratory chain (Mackey 1996, Newman 2013). It typically presents in young adults, mostly men, as painless acute or subacute visual failure of both eyes in quick succession. The estimated prevalence is approximately 2.2 per 100,000 (Mascialino et al., 2012) and LHON is thus an Orphan Disease according to EU and US criteria. Clinically, the acute phase of the disease begins with blurring of central vision and colour de-saturation that affect both eyes. After the initial symptoms, both eyes are usually affected within two to four months from disease onset. Within 12 months of visual loss in one eye, over 97% of patients will have second eye involvement. The central visual acuity deteriorates to the level of counting fingers in up to 80% of cases. Following the nadir, acuity may improve. The degree of improvement is dependent, in part, also on the precise genetic mutation of affected patients. With disease progression, individuals then proceed into the atrophic phase and are usually legally blind for the rest of their lives with a permanent large centrocecal scotoma (Sadun et al., 2011).

Idebenone 2-(10-hydroxydecyl)-5,6-dimethoxy-3-methyl-cyclohexa-2,5-diene-1,4-dione has been suggested to be effective in by-passing the complex I deficiency resulting from the mtDNA point mutations and maintaining cellular energy production by stimulating the alternative pathway through complexes II and III (Haefeli et al., 2011). This activity may also reduce the production of reactive oxygen species (ROS) associated with complex I deficiency and to protect cell membranes and mitochondria from oxidative damage. This provides a strong rationale for its use in LHON (summarized in Gueven and Faldu, 2013; Gueven, 2014).

Detailed information on the medicinal product and on non-clinical data is available in the Investigator's Brochure (IB).

1.2 Rationale for the Study

The randomized, placebo-controlled RHODOS (SNT-II-003) trial (Klopstock et al., 2011), the retrospective cohort study of Carelli et al., (2011), Santhera's ongoing Expanded Access Program (EAP) and several case reports (summarized in Gueven and Faldu, 2013), provide evidence that idebenone promotes the recovery of VA in patients with LHON. However, due to the nature of these datasets, this evidence is not considered comprehensive.

In view of the urgent medical need and poor prognosis of LHON if untreated, a randomized, placebo-controlled study to provide comprehensive data is not considered feasible in LHON. An open-label study is therefore considered the most appropriate strategy for gathering additional evidence for the efficacy of idebenone in the treatment of LHON. The primary objective of this study is therefore to compare the outcomes for patients treated with idebenone ≤1 year of the onset of symptoms in this study with those of matching untreated patients from an external natural history control group generated in a historical case record survey (CRS).

In RHODOS, LHON patients enrolling up to 5 years after the onset of symptoms of disease were treated with idebenone. Whilst natural history VA outcomes data collected from LHON patients early in the course of the disease is available, relatively little reliable natural history VA outcomes data is available from patients with longer disease durations. The primary endpoint of this study will therefore compare the VA outcomes for patients treated with idebenone ≤1 year of the onset of symptoms with matching natural history control data. Secondary endpoints will include outcomes for patients treated with idebenone >1 year after the onset of symptoms. Since LHON

is known to lead to the apoptotic loss of retinal ganglion cells where the extent of loss increases with time since onset of disease, this study will explore further the relationship between time since onset at the initiation of idebenone therapy and CRR, where possible compared to untreated control patients.

The treatment duration in RHODOS was 6 months and a larger proportion of idebenone-treated patients presented with CRR in VA compared to placebo. However, data from Santhera's ongoing Expanded Access Program (EAP) indicates that prolonged treatment can increase both the proportions of patients with CRR of VA and the magnitude of the recovery observed.

Proportions of Patients and Eyes in the EAP with CRR from VA Nadir following 6 months and 12 months of treatment

CRR from Nadir in the Efficacy Population	Patients		Eyes		Treatment duration at assessment [months]			
	all	CRR	all	CRR	*mean*	*(SD)*	*min*	*max*
Patients with		**CRR at 6m**		**CRR at 6m**				
6m assessment available	62	19 (30.6%)	124	30 (24.2%)	5.8	(1.0)	3.1	8.1
		CRR at 12m		**CRR at 12m**				
12m assessment available	47	17 (36.2%)	94	28 (29.8%)	11.6	(1.3)	9.1	13.9
		CRR at last obs.		**CRR at last obs.**				
at last observation	69	34 (49.3%)	138	55 (39.9%)	15.4	(9.0)	2.8	36.2

6m assessment : closest to 6 months, values at 3-9 months considered

12m assessment : closest to 12 months, values at 9-15months considered

Source Tables : EAP 01-01, EAP 01-02, EAP 01-03, EAP 02-01, EAP, 02-02, EAP 02-03

Magnitude of Recovery in Eyes in the EAP with CRR from VA Nadir at the 6 month, 12 month or at the last observation

Recovery* from Nadir [logMAR]**	N	mean	SD	median	max	min
at the 6 month vist	15	-0.47	0.31	-0.38	-1.00	-0.14
at the 12 month vist	15	-0.62	0.48	-0.40	-1.40	-0.10
at last observation (mean treat. dur. 20.9 m)	15	-0.93	0.42	-1.08	-1.44	-0.14

**for eyes with CRR from BL where recovery had occured at the 6 months visit and a 12 month visit was available, too*

***off chart set to 1.70 [logMAR]*

Note, for these 15 eyes the VA at BL was also the VA at Nadir

Furthermore, data from the RHODOS and from the EAP provide evidence that the LHON-causative mutation harboured is prognostic of CRR in VA.

Therefore, secondary objectives of this study are to provide information on the effect of treatment duration on both the proportions of patients presenting with CRR and on the magnitude of any response with increasing treatment time and on the influence of the mutation harboured on CRR rate compared to spontaneous CRR (sCRR) untreated control patients.

The study will also allow the assessment of the safety and tolerability of long-term treatment with idebenone, with particular emphasis on the proportion of patients experiencing elevated Liver Function Tests (LFTs) or changes in blood cell counts.

2 Study Objectives and Endpoints

2.1 Study Objectives

2.1.1 Primary Objective

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

2.1.2 Secondary Objectives

- To assess efficacy of idebenone in the promotion of recovery or stabilization of vision in LHON patients treated with idebenone >1 year after the onset of symptoms, compared to an external natural history control group of idebenone naive patients
- To compare the promotion of recovery or stabilization of visual acuity in LHON patients treated with idebenone ≤1 and >1 year after the onset of symptoms
- To assess the influence of mutation on the promotion of recovery or stabilization of visual acuity in LHON patients treated with idebenone
- To assess the influence of time since onset of symptoms prior to the initiation of treatment with idebenone on the promotion of recovery or stabilization of visual acuity in LHON patients
- To assess the influence of duration of treatment with idebenone on changes in visual acuity in LHON patients
- To assess safety of long-term treatment of LHON patients with idebenone.

2.2 Study Endpoints

2.2.1 Primary Endpoint

- Proportion of eyes with clinically relevant recovery of VA from Baseline or in which Baseline VA better than 1.0 logMAR was maintained at Month 12 in patients treated with idebenone ≤1 year after the onset of symptoms, compared to matching external natural history control group

Clinically Relevant Recovery (CRR) is defined as a change from “off-chart” visual acuity (VA) to at least 1.6 logMAR value or an improvement of at least 0.2 logMAR value within “on-chart”.

2.2.2 Secondary Endpoints

- Components of the primary endpoint:
  - Proportion of eyes with CRR of VA from Baseline at Month 12 compared to matching external natural history control group
  - Proportion of eyes in which Baseline VA better than 1.0 logMAR was maintained at Month 12 compared to matching external natural history control group.
- Proportion of eyes in patients treated with idebenone >1 year after the onset of symptoms with CRR of VA from Baseline or in which Baseline VA better than 1.0 logMAR was maintained at Month 12 compared to external natural history control group, in all patients and classified by mutation
- Proportion of eyes and patients treated with idebenone ≤1 year after the onset of symptoms with CRR of VA from Baseline or in which Baseline visual acuity better than 1.0 logMAR was maintained following 6, 18 and 24 months of treatment with idebenone compared to matching external natural history control group, in all patients and classified by mutation

- Proportion of eyes/patients treated with idebenone ≤1 year or >1 year after the onset of symptoms with “Off-chart” VA at Baseline in whom VA improves to better than 1.60 logMAR by Month 6, 12, 18 and 24
- Proportion of eyes/patients treated with idebenone ≤1 year or >1 year after the onset of symptoms with VA in the categories of better than 1.0 logMAR, 1.0 to 1.68 logMAR and above 1.68 logMAR at each assessment time point up to Month 24
- Safety as assessed by AE count and laboratory analyses during the study

3 Study Design

3.1 Summary of Study Design

The study will be an open-label interventional study requiring 80 patients enrolled ≤1 year after the onset of symptoms to complete the 12 month treatment period (for evaluation of the primary endpoint), and 80 patients enrolled >1 year after the onset of symptoms to complete the 12 month treatment period (for evaluation of the secondary endpoints in these patients).

This multinational study is conducted with one protocol for sites under the IND (U.S. sites) in compliance with the IND requirements contained in 21 CFR 312, and a different version of the protocol for foreign sites not under the IND. As the intent is to pool the data from U.S. and foreign sites, it is ensured, as required, that the protocol versions are very similar or identical.

Patient eligibility for enrolment will be determined during the Baseline (Visit 1). Beginning at Baseline (Visit 1), the patient will receive study medication to take at home and will undergo regular assessments in the clinic throughout the study period until Visit 8 (Month 24) at which time the study medication is withdrawn. For all patients, there will be a final follow-up 28-35 days after study medication withdrawal. Patients enrolled in the study will commence study medication intake on the first day after the Baseline visit.

3.2 Trial Treatment, Dosage and Regimen

Enrolled patients will receive idebenone 900 mg/day (2 x 150 mg tablets to be taken orally 3 times daily with meals) according to the IB.

3.3 Duration of Subject Participation

Patient’s participation will last approximately 25 months: 24-month treatment phase and an approximately 1 month follow-up phase.

4 Selection of Subjects

4.1 Inclusion Criteria

The following criteria should be assessed during Baseline Visit. If any does not apply, the patient must not be included in the study:

1. Impaired visual acuity in affected eyes due to LHON
2. No explanation for visual loss besides LHON
3. Age ≥ 12 years
4. Onset of symptoms ≤5 years prior to Baseline
5. Confirmation of either G11778A, G3460A or T14484C LHON mtDNA (for the ITT population, not required for enrolment)
6. Written informed consent obtained from the patient
7. Ability and willingness to comply with study procedures and visits
8. Women of Childbearing Potential (WCBP) who have a negative urine or serum pregnancy test at Baseline visit and who are willing to use a highly effective contraceptive measure and maintain it until treatment discontinuation.

4.2 Exclusion Criteria

The following criteria should be checked during Baseline Visit. If any applies, the patient must not be included in the study:

1. Patient has provided natural history data to the Case Record Survey (SNT-CRS-002)
2. Any previous use of idebenone
3. Any other cause of visual impairment (e.g. glaucoma, diabetic retinopathy, AIDS related visual impairment, cataract, macular degeneration, etc.) or any active ocular disorder (uveitis, infections, inflammatory retinal disease, thyroid eye disease, etc.)
4. Known history of clinically significant elevations (greater than 3 times the upper limit of normal) of AST, ALT or creatinine
5. Patient has a condition or is in a situation which, in an investigator's opinion may put the patient at significant risk, may confound study results or may interfere significantly with the patient's participation in the study
6. Participation in another clinical trial of any investigational drug within 3 months prior to Baseline
7. Hypersensitivity to the active substance or to any of the following excipients: Lactose monohydrate, Microcrystalline cellulose, Croscarmellose sodium, Povidone K25, Magnesium stearate, Colloidal silica, Macrogol 3350, Poly(vinyl alcohol), Talc, Titanium dioxide, Sunset yellow FCF (E110).
8. Women who are pregnant or have a positive pregnancy test at Baseline visit
9. Women who are breastfeeding

4.3 Life Style Guidelines

With the exception of the criteria described in section 4.4, there are no particular lifestyle recommendations. However all smoking patients will be advised that smoking is a special risk factor for LHON and will be counselled by the investigator regarding smoking cessation.

4.4 Pregnancy and lactation

Although animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, women who are pregnant or have a positive pregnancy test at Baseline visit and women who are breastfeeding will be excluded from the study.

For women who are breastfeeding, a decision must be taken to discontinue breastfeeding or be excluded from the study.

Furthermore, WCBP can be included in the study if they have a negative urine or serum pregnancy test at Baseline visit and are willing to use a highly effective contraceptive measure and maintain it until treatment discontinuation.

The Clinical Trial Facilitation Group recommendations should be taken into account as guidance for the contraception methods to be used for WCBP enrolled in this trial (see also section 8.6.4).

5 Study Medication and Administration

5.1 Drug Supplies

The study medication must not be used for any purpose other than that described in this protocol.

5.1.1 Formulations

Idebenone is developed and manufactured by Santhera Pharmaceuticals (Switzerland) Ltd. and will be provided as 150 mg film-coated tablets.
Ingredients: idebenone, Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium, Povidone (k = 25), Magnesium Stearate, Colloidal silica, Coating (Macrogol/PEG 3350, Polyvinylalkohol, Titanium Dioxide, Talc, Sunset yellow FCF (E110)).

5.1.2 Packaging and Labelling

The study medication will be provided in bottles with 180 tablets.

Patients will receive study medication at Visit 1 through Visit 7. Patients will receive 2 bottles at Visit 1, 3 bottles at Visit 2, 4 bottles at Visits 3 through Visit 5 and 7 bottles at Visit 6 and Visit 7. Each bottle contains 180 tablets, the medication for 30 days. Up to 31 bottles will be assigned to each patient.

The labelling encompasses the information according to GMP guideline Volume 4, Annex 13 for Investigational Products and the local laws and 21 CFR Section 312.6 – Labelling of an investigational new drug.

5.1.3 Supplies

The sponsor will supply the investigator with enough study medication to administer sufficient doses to all patients as described in the present protocol. Additional material will be supplied for replacement in case of damage or inappropriate storage conditions. All medication needs to be accounted for on the form provided.

Under no circumstances is it permitted to use the study medication for purposes other than those specified in this protocol.

5.1.4 Storage

Investigators must store study medication in a safe, controlled place with no access for unauthorized personnel. Study medication must be stored under the conditions shown in the

label. Study medication will be stored at the study site or pharmacy according to legal requirements.

Investigators will provide patients with instructions on how to use and store medication at home.

5.2 Dosage and Administration

Patients are dispensed enough medication to last until the next scheduled visit. All patients will be instructed to take study medication as follows:

- 2 tablets 3 times daily with meals, totalling 6 tablets a day

Patients will document in the patient diary, on a daily basis, the medication they have taken.

5.3 Treatment

All patients receive idebenone study drug at the same dose; there is no randomization process.

5.4 Replacement of Unusable Study Medication

In addition to the materials for the planned number of patients, additional bottles will be supplied to replace any that are damaged or lost. The investigator should replace any lost/missing bottle with a replacement bottle. The sponsor need not be notified immediately in these cases. However, documentation of the use of the replacement bottle and reason for using it must be recorded by the investigator.

If the patient loses any study medication, or finds that some medication is unusable, he/she must contact the investigator immediately. The investigator will replace the study medication as necessary, documenting the replacement, as above.

5.5 Method of Blinding / Breaking the Blind

This is an open label study; no blinding implemented.

5.6 Compliance and Accountability

Patients will document medication taken, on a daily basis, in the patient diary.

At each visit, the patient will be asked to return all unused study medication and all bottles to the investigator. Medication will be inventoried and treatment compliance will be calculated as a percentage by dividing the number of tablets taken by the number of days since the previous visit multiplied by six, multiplied by 100. If the compliance lies outside of the range of 80-120%, inclusively, the sponsor must be consulted to decide whether or not the patient should continue in the study.

5.7 Site Accountability of Study Drug

At any time the figures of supplied, used and remaining medication should match. At the end of the study, it must be possible to reconcile delivery records with those of used and unused stocks. Account must be given of any discrepancies.

5.8 Return or Destruction of Study Medication

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

After approval from Santhera Pharmaceuticals (Switzerland) Ltd, unused study medication should be destroyed in accordance with the applicable local law and can either be returned to Santhera or destroyed at the investigational site. Documentation of destruction of the study drug must be forwarded to the sponsor.

6 Conduct of Study

6.1 Outline of Study Procedures

All study procedures are outlined in the Schedule of Assessments shown below. A more detailed description of the study procedures performed at each visit is given in the following sections of the protocol.

Patients will be enrolled to receive 900 mg idebenone (2 tablets 3 times daily with meals) for 24 months. Starting with Baseline/Visit 1 sufficient study medication will be dispensed to last until the next visit. The patient will take the first dose of study medication on Day 1, the day of the Baseline Visit (or as instructed by the site investigator / study nurse).

The duration of study participation for each individual patient will be approximately 25 months and comprise 9 study visits (V1-V9). Before any study-specific procedures are undertaken, the patient (and parent/legal guardian if required) will have been thoroughly informed by the investigator of the purpose of the study, the relevant procedures and of patient rights and responsibilities. Patient information will be distributed in writing and signatures of consent obtained on the consent form. (See also Section 10.3).

Patient enrolled in the study will receive study medication at Baseline/Visit 1; the first study medication intake is on the day of the Baseline/Visit 1 (or as instructed by the site investigator / study nurse). During the 24 month treatment period, visits take place at Month 1, Month 3, Month 6, Month 9, Month 12, Month 18 and Month 24. Visit 8 (Month 24) is the endpoint of treatment. Visit 9 is a follow-up, 28-35 days after study medication discontinuation.

Physical examination and measurement of vital signs will be undertaken at Baseline/Visit 1 and then at Visit 4/Month 6, Visit 6/Month 12, Visit 7/Month 18 and Visit 8/Month 24.

Safety blood and urine and safety assessments will be done at each visit.

A urine or serum pregnancy test will be performed for WCBP at the baseline visit and further when clinically indicated.

Assessment of VA (assessed by ETDRS charts and reported in logMAR value) will be done at every visit.

During the Baseline visit the diagnosis of LHON will be confirmed and other eye diseases excluded. This will require fundoscopy with dilated pupils to be performed at the Baseline visit and every 12 months thereafter. Blood sample will be taken for the genetic analysis, if the genetic diagnosis of the patient is not confirmed at the Baseline visit. The report from the genetic analysis will need to be on file prior to Visit 4.

Should the genetic diagnosis reveal that a patient does not harbour a LHON-specific mtDNA mutation, the patient will be withdrawn from the study.

It should be noted however that the VA outcomes for patients carrying one of the three major LHON-specific mtDNA mutations (G3460A, G11778A or T14484A) will be used in the primary analyses.

The following study procedures are performed at Baseline/Visit 1: physical exam, vital signs, weight, safety blood and urine sampling and a urine or serum pregnancy test for WCBP. The investigator should ensure that the results of the safety blood and urine analyses and pregnancy

test are reviewed and approved during Visit 1. The patient will be informed by the investigator or study nurse by phone should these results not be available at the day of Visit 1/Baseline.

Patients and/or parents/legal guardians will monitor safety throughout the study at home, and will document any adverse events (AEs), or other relevant findings in a patient diary.

Patient and/or the parent/legal guardian will be instructed to contact the investigator immediately should the patient manifest any signs or symptoms perceived as serious during the period extending from the day of signature of the consent form up to and including the last visit. After this period of time, the investigator should report to the sponsor only AEs that are serious and considered related to the study medication.

Information about AEs or serious adverse events (SAEs) will be collected throughout the study period and followed up as referred to in Sections 8.1 – 8.3 of this protocol.

6.2 Schedule of Assessments

	Visit 1 / Baseline Day 1	Visit 2 / Month 1 *(± 1 week)*	Visit 3 / Month 3 *(± 1 week)*	Visit 4 / Month 6 *(± 1 week)*	Visit 5 / Month 9 *(± 1 week)*	Visit 6 / Month 12 *(± 1 week)*	Visit 7 / Month 18 *(± 1 week)*	Visit 8 / Month 24 *(± 1 week)*	Visit 9 / Follow-Up Visit (28-35 days after drug discontinuation)
Informed Consent	X								
Inclusion/Exclusion criteria	X								
Genetic Analysis Blood Sampling	X								
Medical History	X								
Demographics	X								
Physical Exam, height & weight (V1 only)	X			X		X	X	X	
Vital Signs (1)	X			X		X	X	X	
Urine or serum pregnancy test (for WCBP)	X	X (3)							
Safety Blood Sampling	X	X	X	X	X	X	X	X	X
Safety Urine Analysis	X	X	X	X	X	X	X	X	X
Fundoscopic Exam	X					X		X	*X (optional)*
Visual Acuity (logMAR)	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X
Distribution of Patient Diary	X	X	X	X	X	X	X	X	
Collection of Patient Diary		X	X	X	X	X	X	X	X
Dispensing of Study Medication	X (2)	X	X	X	X	X	X		
Collection of Residual Study Medication		X	X	X	X	X	X	X	
Patient Compliance		X	X	X	X	X	X	X	
End of Study									X

(1) Heart rate and blood pressure in supine position, respiratory rate in supine position.
(2) First administration of study medication to be on Day 1 (day of Baseline visit or when approved by the investigator/study nurse).
(3) When clinically indicated.

6.2.1 Visit 1 / Baseline (Day 1)

Baseline assessments include:

Informed Consent
Medical History and confirmation of LHON (blood sample for genetic testing)
Demographic characteristics
Inclusion/Exclusion criteria
Physical Examination (including height & weight)
Vital Signs
Safety Blood analysis
Safety Urine analysis
Urine or serum pregnancy test for WCBP
Fundoscopic Exam
Visual Acuity (logMAR)
Concomitant Medication
Distribution of Study Medication
Distribution of Patient Diary

6.2.2 Visit 2 / Month 1 (± 1 week)

Assessments include:

Safety Blood analysis
Safety Urine analysis
Visual Acuity (logMAR)
Urine or serum pregnancy test for WCBP when clinically indicated
Assessment of Adverse Events
Concomitant Medication
Patient Compliance
Collection and Distribution of Study Medication
Collection and Distribution of Patient Diary

6.2.3 Visit 3 / Month 3 (± 1 week)

Assessments include:

Safety Blood analysis
Safety Urine analysis
Visual Acuity (logMAR)
Urine or serum pregnancy test for WCBP when clinically indicated
Assessment of Adverse Events
Concomitant Medication
Patient compliance
Collection and Distribution of Study Medication
Collection and Distribution of Patient Diary

6.2.4 Visit 4 / Month 6 (± 1 week)

Assessments include:

Physical Examination
Vital Signs
Safety Blood analysis
Safety Urine analysis
Visual Acuity (logMAR)
Urine or serum pregnancy test for WCBP when clinically indicated
Assessment of Adverse Events

Concomitant Medication
Patient compliance
Collection and Distribution of Study Medication
Collection and Distribution of Patient Diary

6.2.5 Visit 5 / Month 9 (± 1 week)

Assessments include:

Safety Blood analysis
Safety Urine analysis
Visual Acuity (logMAR)
Urine or serum pregnancy test for WCBP when clinically indicated
Assessment of Adverse Events
Concomitant Medication
Patient compliance
Collection and Distribution of Study Medication
Collection and Distribution of Patient Diary

6.2.6 Visit 6 / Month 12 (± 1 week)

Assessments include:

Physical Examination
Vital Signs
Safety Blood analysis
Safety Urine analysis
Fundoscopic Exam
Visual Acuity (logMAR)
Urine or serum pregnancy test for WCBP when clinically indicated
Assessment of Adverse Events
Concomitant Medication
Patient compliance
Collection and Distribution of Study Medication
Collection and Distribution of Patient Diary

6.2.7 Visit 7 / Month 18 (± 1 week)

Assessments include:

Physical Examination
Vital Signs
Safety Blood analysis
Safety Urine analysis
Visual Acuity (logMAR)
Urine or serum pregnancy test for WCBP when clinically indicated
Assessment of Adverse Events
Concomitant Medication
Patient compliance
Collection and Distribution of Study Medication
Collection and Distribution of Patient Diary

6.2.8 Visit 8 / Month 24 (± 1 week)

Assessments include:

Physical Examination
Vital Signs
Safety Blood analysis

Safety Urine analysis
Fundoscopic Exam
Visual Acuity (logMAR)
Urine or serum pregnancy test for WCBP when clinically indicated
Assessment of Adverse Events
Concomitant Medication
Patient compliance
Collection of Study Medication
Collection and Distribution of Patient Diary

6.2.9 Visit 9 / Follow-Up Visit (28-35 days after study drug discontinuation)

Assessments include:

Safety Blood analysis
Safety Urine analysis
Visual Acuity (logMAR)
Fundoscopic Exam (optional)
Assessment of Adverse Events
Concomitant Medication
Collection of Patient Diary

6.3 Concomitant Medication / Treatment

At each study visit, the investigator will review the patient diary and question the patient and/or the patient's caregiver about any medication taken. All concomitant medications, including vitamins and supplements, will be recorded in the patient's CRF with details of dose, route of administration, dates of administration and indication.

The period for documentation of concomitant medication begins on the day of the Baseline Visit and ends on the day of the final study visit. Medication discontinued before the Baseline Visit should not be recorded in concomitant medication log in the CRF. Medication concomitant with an SAE reported after the final study visit should be listed on the SAE form.

6.3.1 Prohibited Concomitant Medication

Intake of the following medication will lead to withdrawal from the study:

- any other investigational drug
- any other source of idebenone

Any case of doubt should be discussed with the Sponsor's Medical Monitor and the outcome confirmed in writing.

6.3.2 Interaction with other medicinal products

Idebenone is a weak inhibitor of CYP3A4 and therefore sensitive substrates with narrow therapeutic window such as alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution (please refer to the Idebenone Investigator's Brochure with indication area: Neuro-Ophthalmology).

6.4 Study Completion

A patient is considered to have completed the study if he/she has taken the study medication for 24 months and attended Visit 8/Month 24. These results will be documented for each patient in the study. Completion or discontinuation of the study will be documented in the patient's CRF.

6.5 Discontinuation / Withdrawal

6.5.1 Conditions for discontinuation/withdrawal

Reasons that a patient may be withdrawn from the study include the following:

- adverse event(s)
- major protocol deviation/violation (e.g. Intake of any prohibited concomitant medication as listed in Section 6.3)
- inclusion criteria not met/exclusion criteria met
- genetic diagnosis reveals that a patient does not harbour a LHON-specific mtDNA mutation
- pregnancy
- lack of compliance with study medication
- patient withdrew consent
- lost to follow-up
- death
- other (reason to be documented)

Each patient has the right to withdraw from the trial at any time for any reason without affecting the right to treatment by the investigator. The investigator also has the right to withdraw the patient if he/she judges it in the patient's best medical interest. In either case, all attempts should be made to document the reason for withdrawal. Santhera Pharmaceuticals (Switzerland) Ltd reserves the right to request the withdrawal of a patient due to protocol deviation, administrative or other reasons.

It is understood by all concerned that an excessive rate of withdrawals can render the study non interpretable, therefore every effort should be made to avoid unnecessary withdrawals. However, WHENEVER a patient is withdrawn from a trial, FOR WHATEVER REASON, a final study evaluation must be completed for that patient, including all Visit 9 evaluations if possible, and stating the reasons why the patient was withdrawn. All documentation concerning the patient must be as complete as possible. Withdrawals due to non-attendance must be followed-up by the investigator to obtain the reason for non-attendance.

6.5.2 Procedures for Handling Discontinued Patients

Investigators should make every attempt to contact those patients who do not return for scheduled visits or follow-up.

Whenever a patient is withdrawn from the study, all efforts should be made to complete and report the observations as thoroughly as possible. A final evaluation must be completed for that patient, including all Follow-up Visit evaluations (see Section 6.5.1) if possible, and documenting the reasons why the patient was withdrawn from the trial.

Withdrawals due to intercurrent illnesses or AEs must be fully documented in the CRF with the addition of supplementary information if available and/or appropriate. Withdrawals due to non-attendance must be followed-up by the investigator to obtain the reason for non-attendance.

Information gathered should be described on the End of Study page of the CRF and on the appropriate forms (i.e., Adverse Events, Concomitant Medication).

Withdrawn patients will not be replaced.

6.6 Treatment and Storage of Biological Samples

6.6.1 Safety Blood and Urine Samples

Measurement tests for safety blood and urine analysis will be performed by the local laboratory according to their standard procedures.

7 Efficacy Assessments

7.1 Visual acuity

Visual acuity in both eyes will be assessed at every visit by a specialist in ophthalmology. Patients will be refracted to ensure that, at every study visit, optimum vision at 4 meters is achieved. When measuring acuity in the right eye the left eye is covered and the patient is asked to read down logMAR chart 1 slowly letter by letter. When a letter is read correctly the examiner indicates this on the score sheet (identical to the chart layout). Only one reading of a given letter is allowed. When the patient has difficulty, he or she is encouraged to guess. The distance to the chart is 4 meters. If, however, less than 20 letters are read correctly from the 4 meter rows, the patient's distance to the chart will be reduced to 1 meter and the logMAR score is assessed at this distance in the same manner. Should the patient not be able to read any letters, the investigator will proceed to record whether VA is reduced to counting fingers (CF), hand motion (HM), light perception (LP), or no light perception. CF and HM are tested at a distance of about 30 cm from the eye. The left eye will then be tested in the same way using chart 2.

8 Safety Evaluations

8.1 Adverse Events (AEs)

The recording of AEs is an important aspect of study documentation. It is the responsibility of the Investigator to document all AEs according to the detailed guidelines set out below.

The patient and/or his caregiver will be instructed to contact the Investigator immediately should the patient manifest any signs or symptoms perceived as serious during the period extending from the day of signature of the consent form up to and including the last visit. After this period of time, the Investigator should report to the sponsor only AEs that are serious and related to the study medication.

8.1.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. This includes any noxious, pathological or unintended change in anatomical, physiological or metabolic functions as indicated by physical signs, symptoms and/or laboratory detected changes occurring in any phase of the study whether considered related to the study medication, or not.

Exacerbation of pre-existing conditions or events, intercurrent illnesses, drug-drug or drug-food interactions, lack of efficacy, overdose, drug maladministration or accidental exposure, and dispensing errors should also be considered and reported as AEs (as SAE if they result in a Serious Adverse Event, see Section 8.2). Discrete episodes of chronic conditions occurring during the study period should be reported as AEs in order to assess changes in frequency or severity.

Anticipated day-to-day fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation need not be considered as AEs. Pre-existing conditions should be re-assessed throughout the study and recorded as AE or SAE only if the frequency, severity, or character of the condition worsens.

AEs should be documented in terms of diagnosis whenever possible; if a diagnosis is not yet available, signs and symptoms should be reported in the Adverse Event page of the CRF.

AEs, regardless of seriousness, which occur prior to the day of signature of the consent form, will be documented in the Medical History form within the patient's CRF.

Hospitalization should not be considered as an AE (therefore also not an SAE) when it is due to:

- Medical or surgical procedures planned before study entry;
- Medical or surgical procedures for pre-existing medical conditions which did not increase in frequency, severity, or nature following initiation of the study;
- Social or economic reasons.

These cases must be recorded on the Hospitalization form of the CRF.

8.1.2 Adverse Events of Special Interest (AESI)

The detection, monitoring and evaluation of potential risks of idebenone are addressed in the idebenone risk management plan. AESI correspond to the important potential risks which are identified in the safety specification and listed in the Risk Management Plan and in the corresponding interface between the European Risk Management Plan and EudraVigilance. Important potential risks are important risks for which there is some basis for suspicion of a causal association with the medicinal product of interest but where this association has not been confirmed and needs further confirmed or rejected as new data on come available. Currently, there are no important identified risks, i.e. important risk for which there is adequate evidence of an association with the medicinal product of interest, listed in the idebenone RMP.

Therefore, particular attention should be paid to AESI that are described as follows as follows in this RMP and constitute important potential risks for idebenone:

- Abnormal liver function test (ALT, AST, total bilirubin, GGT) or hepatitis (liver disease)
- Blood count abnormalities (such as agranulocytosis, anaemia, leukocytopenia or thrombocytopenia)

In order to be considered as AESI, the events should in first place qualify as AE according to the guidance presented in 8.1.1 above.
Possible fluctuations of hepatic laboratory tests or blood count values which from medical history may be expected in the patient but which are not considered clinically relevant by the investigator should not be reported as AESI.
For hepatic laboratory tests listed above any change below 1.5XULN usually are considered not to be clinically relevant, but this qualification as not clinically relevant should always remain a judgment by the investigator in the individual patient.
For complete and accurate safety surveillance, the data collected on these pre-defined events will include as many details as possible to corroborate diagnosis.
AESI should be reported using the designated section of the SAE report form and transmitted to UBC with 24 hours of learning of its occurrence, regardless severity and seriousness assessment.

8.1.3 Surveillance Period for Occurrence of Adverse Events

All AEs occurring from the day of signature of the consent form to the date of last visit must be recorded on the Adverse Event page in the patient's CRF, irrespective of severity or whether or not considered related to study medication.

After this period of time, the investigator should report to the sponsor only AEs that are serious and related to the study medication (see Sections 8.2.2-8.2.4).

8.1.4 Recording Adverse Events

The occurrence of AEs should be sought by non-directive questioning of the patient and/or his caregiver at each visit or phone call during the study. AEs also may be detected when they are

volunteered by the patient during or between visits, or through physical examination, laboratory test, or other assessments. All AEs either observed by the Investigator or one of his clinical collaborators, or spontaneously reported by the patient or his caregiver will be evaluated by the Investigator.

The nature of each event, date and time (where appropriate) of onset, severity, relationship to study medication and outcome should be established. Details of any symptomatic/corrective treatment should be recorded on the appropriate page of the CRF.

All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study medication dosage adjusted or temporarily interrupted; study medication permanently discontinued due to this AE; drug therapy given; non-drug therapy given. The action taken to treat the AE should be recorded on the Adverse Event page of the CRF.

Once an AE is detected, it should be followed up until its resolution or until the last study visit. An assessment should be made at each visit (or more frequently, if necessary) of any changes in its severity, its suspected relationship to the study medication, the interventions required to treat it, and the outcome; this information should be recorded on the appropriate page of the CRF. If an AE changes significantly in severity during the study, a new record should be started (see also Section 8.1.7).

8.1.5 Assessment of Severity

The severity of each AE should be assessed as described in the following table:

Assessment	Definition
Mild:	The AE causes discomfort but **no disruption of normal daily activities**, or results in clinically significant but mild abnormalities of laboratory and/or instrumental parameters. It is transient and recovers with or without treatment.
Moderate:	The AE causes significant discomfort, **disrupts normal daily activities** or results in clinically significant and marked abnormalities of laboratory and/or instrumental parameters. It requires treatment.
Severe:	The AE causes severe discomfort, **prevents regular activities** or results in clinically dangerous abnormalities of laboratory and/or instrumental parameters. It may be resistant to treatment or require discontinuation of the study medication.

8.1.6 Assessment of Causality

Complete and accurate information is of critical importance to allow a meaningful causality assessment. Every effort should be made by the Investigator to explain each AE and assess its causal relationship if any, to study medication. Factors that should be evaluated include (but are not limited to):

- Previous observations or reports of similar events during treatment with the study medication
- Previous observations or reports of similar events during treatment with drugs of the same pharmacological class
- Evidence of a plausible pharmacological mechanism
- Causative or contributing role of the underlying disease
- Evidence of similar or related conditions in the patient's medical history

- Causative or contributing role of concomitant medications (if administered)
- Causative or contributing role of a protocol required procedure

Investigators should refer to the Reference Safety Information section of the Investigator's Brochure for a list of AEs that have been observed in clinical trials of idebenone and are thought to be associated its administration.

On the basis of the available evidence, the Investigator should assess the causality of each AE by answering the following question:

In your opinion, is there a reasonable possibility that the AE may have been caused by the study medication?

No = Unrelated / Not-Suspected: the study medication is not suspected to reasonably possibly have contributed to the AE. The reported event can be explained by other and more likely aetiologies.

Yes = Related / Suspected: the study medication is suspected to reasonably possibly have contributed to the AE. There is no evidence of plausible alternative aetiologies or they are considered to constitute insufficient or possibly non-exclusive causes for the reported event.

8.1.7 Follow-up of Adverse Events and Assessment of Outcome

Investigators should follow-up AEs until resolution or until the last study visit, and an assessment should be made at each visit (or more frequently, if necessary) of any changes in its severity, its suspected relationship to the study medication, the interventions required to treat it, and the outcome; this information should be recorded in the CRF.

If the severity of an AE changes significantly during the study period, a new record should be started indicating the change in severity.

The outcome of each AE should be assessed as follows:

- Resolved
- Resolved with sequelae
- Ongoing at patient study conclusion
- Fatal
- Lost to follow up

For follow-up of SAEs, see also Section 8.2.4.

8.2 Serious Adverse Events

8.2.1 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence or effect at any dose, that:

- Results in death,
- Is life threatening*,
- Results in persistent or significant disability/incapacity†,
- Requires in-patient hospitalization‡ or prolongation of existing hospitalization,
- Is a congenital anomaly/birth defect in the offspring of a study patient,
- Is deemed, by the investigator, an important medical event that may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

* Life threatening - definition: An AE is life threatening if the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

† Disabling/incapacitating - definition: An AE is incapacitating or disabling if the event results in a substantial disruption of the patient's ability to carry out normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhoea, influenza, or accidental trauma (e.g. sprained ankle).

‡ Hospitalization - definition: In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for treatment that would not have been appropriate in the physician's office or out-patient setting.

Hospitalization should not be considered as an AE (therefore also not an SAE) when it is due to:
- Medical or surgical procedures planned before study entry;
- Medical or surgical procedures for pre-existing medical conditions which did not increase in frequency, severity, or nature following initiation of the study;
- Social or economic reasons.

These cases must be recorded on the Hospitalization form of the CRF.

When in doubt as to whether an AE should be considered serious or not, the AE should be reported as SAE (= within 24 hours).

8.2.2 Reporting Serious Adverse Events and AESIs

The investigator must report all SAEs/AESIs within 24 hours of becoming aware of the event, whether or not the SAE/AESI is considered to be related to the study medication.

The appropriately completed SAE form (see Guidelines for Completing Serious Adverse Event (SAE) Forms) must be faxed or scanned and emailed to sponsor's designee (see contact details below), who will acknowledge receipt within 1 working day. This initial notification should include minimal, but sufficient information to permit identification of the reporter, the patient, the suspect study medication, adverse event term, seriousness criteria and the investigator's causality assessment. The investigator should not wait for additional information to fully document the event before sending the initial report.

Each SAE/AESI should be followed-up in order to complete the collection of all missing information and address any relevant query requested by the sponsor. All newly available information collected on follow-up must be submitted to sponsor's designee by faxing or emailing a duly filled-in SAE form within 24 hours from awareness (as for the initial report). The follow-up report should include information often not available at the time of the initial notification, e.g. medical history, concomitant medications, actions taken by the investigator and outcome of the event. Hospital discharge summaries and autopsy reports should be obtained where applicable.

Contact for Safety reporting:	United Biosource Corporation EU Safety Services Phone: +41 22 596 44 44 Fax: +41 22 596 44 46 e-mail: EUSafety@ubc.com

Investigators must report SAEs to the appropriate IRB/ethics committee if requested by the committee and/or according to local legal requirements.

AEs which meet all of the following criteria:
- Serious
- Unexpected
- There is at least a reasonable possibility that there is a causal relationship between the event and the medicinal product

The AEs meeting the above criteria will be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs) and should be reported to the relevant IRB/Ethics Committee and to the relevant Health Authorities in accordance with applicable regulatory requirements for expedited reporting. It is the Sponsor's responsibility to report SUSARs to central Ethics Committee/IRB and relevant Health Authorities, although this responsibility will be delegated to United Biosource Corporation (UBC).

8.2.3 Causality Assessment of Serious Adverse Events

Every effort should be made by the investigator to explain each SAE and assess its causal relationship, if any, to study medication by answering the following question:

In your opinion, is there a reasonable possibility that the SAE may have been caused by the study medication?

> **No = Unrelated / Not-Suspected:** the study medication is not suspected to reasonably possibly have contributed to the SAE. The reported event can be explained by other and more likely aetiologies (please specify which ones).
>
> **Yes = Related / Suspected:** the study medication is suspected to reasonably possibly have contributed to the SAE. There is no evidence of plausible alternative aetiologies or they are considered to constitute insufficient or possibly non-exclusive causes for the reported event.

For further guidance on the assessment of causality, refer to Section 8.1.6.

8.2.4 Follow-up of Serious Adverse Events

All SAEs reported from the date of signature of the consent form to the date of the last study visit must be documented in the SAE form and followed up until the event resolved, subsided, stabilized, disappeared or is otherwise explained or the study patient is lost to follow-up.

Any SAEs experienced after this period should be reported to the sponsor if the investigator suspects a causal relationship to the study medication.

All follow-up activities must be reported, if necessary on one or more consecutive SAE forms in a timely manner. All fields with additional or changed information must be completed and the form should be forwarded to sponsor's designee within 24 hours from the receipt of new information.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

8.3 Treatment of Adverse Events

Treatment of any AE is at the sole discretion of the investigator and according to current available best treatment. The applied measures should be recorded in the CRF of the patient.

8.4 Pregnancy

Women participating in the study who become pregnant while taking study medication will be discontinued as per Section 6.5.1.

Any pregnancy that occurs during the study, or before last study visit, must be recorded on a Clinical Trial Pregnancy form (see Guidelines for Completing Pregnancy Forms) and reported to the sponsor's designee (see contact details above) within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine its outcome (i.e. spontaneous or voluntary abortion, presence or absence of any birth defects, congenital abnormalities, or maternal and/or

newborn complications) and it should include the investigator's assessment of any possible relationship between the outcome and the exposure to the study medication.

Women becoming pregnant while their partner is taking the study medication should be followed-up in order to collect information about the outcome of their pregnancy. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Any SAE experienced during pregnancy (e.g. abortion, abnormal results from fetal examination) must be treated as an SAE and reported within 24 hours from awareness.

8.5 Anthropometric measurements

8.5.1 Weight and height (Visit 1 only)

Weight will be recorded in kilogram (kg), to the nearest 100 grams, using always the same scale.

Height is recorded in centimetres (cm) and measured in an upright position using a stadiometer.

8.6 Safety and Monitoring Measures

8.6.1 Physical Examination and Vital Signs

Physical examination will include assessment of the skin, head, neck, ears, nose, throat, chest, lungs, heart, abdomen, lymph nodes, musculoskeletal system, vascular system, nervous system and any other physical conditions of note.

Blood pressure will be measured in supine position. Supine blood pressure should be measured first after the patient has been lying down for 5 minutes.

Blood pressures will be measured with a standardized mercury manometer; alternative validated methods of measurement may also be used. The point of disappearance of Korotkoff sounds (phase V) will be recorded as the diastolic blood pressure where a sphygmomanometer is used.

Heart rate will be determined over 60 seconds in supine position following the recording of blood pressure.

Respiratory rate will be determined over 60 seconds in supine position following the recording of blood pressure and heart rate.

8.6.2 Fundoscopic Exam

A fundoscopic exam with pupil dilation will be performed at Visit 1/Baseline, Visit 6, and Visit 8 in order to exclude any other underlying diseases that could be responsible for vision loss. An additional fundoscopic exam may be performed at Visit 9 (follow-up visit) if any abnormalities were observed at the previous Visit 8.

8.6.3 Safety Blood Sampling and Urine Analysis

Measurement tests for safety blood and urine analysis will be performed at all visits. Blood samples for haematology, biochemistry and urine analysis will be analysed in local laboratories.

10 ml of blood will be collected for safety haematology and biochemistry at each visit. Urine samples will also be collected at each visit.

Haematology

Safety haematological analysis will include:

- red blood cell count
- hemoglobin
- hematocrit
- red cell indices
- white blood cell count, including differential
- platelet count

Biochemistry

Safety biochemistry will include:

- sodium
- potassium
- chloride
- bicarbonate
- urea
- creatinine
- calcium
- inorganic phosphate
- glucose
- total bilirubin
- total protein
- albumin
- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)
- alkaline phosphatase
- gamma GT (GGT)
- creatine kinase (CK)
- cholesterol
- triglycerides
- uric acid

Urine Analysis

Safety urine analysis will include:

- pH
- protein
- glucose
- ketones
- blood

Pregnancy Test

Pregnancy test can use:

- highly sensitive urine analysis

or

- serum analysis

8.6.4 Highly effective contraceptive measures

Highly effective birth control methods (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal or transdermal) associated with inhibition of ovulation
- Progestogen-only hormonal contraception (oral, injectable or implantable) associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner[1]
- Sexual abstinence[2]

[1] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[2] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments.
The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

8.7 Data Safety Monitoring Board (DSMB)

The DSMB is an independent multidisciplinary group with expertise in the fields of clinical medicine relevant for the study indications, drug safety, and clinical trial statistics. The DSMB

consists of a minimum of three members who have no role in the conduct of the trials, or any other conflict of interest. The DSMB assesses the safety of the interventions during the idebenone clinical development program, by reviewing interim and cumulative safety data. The DSMB provides recommendations about stopping or continuing the clinical development program, including any modifications which may be required to protect the safety of the subjects. The DSMB structure, responsibilities and procedures are described in details in a dedicated charter.

9 Data Evaluation and Statistics

9.1 General Considerations

The present clinical investigation has the primary goal to determine whether administration of idebenone can maintain or improve vision in LHON patients. The investigation will be conducted as a prospective, multicenter, open-label trial.

The following subsections summarize the statistical principles and procedures to be used in the analysis of this study. A more detailed description will be provided in a separate Statistical Analysis Plan (SAP) that will be finalized prior to database lock. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

9.2 Analysis Variables

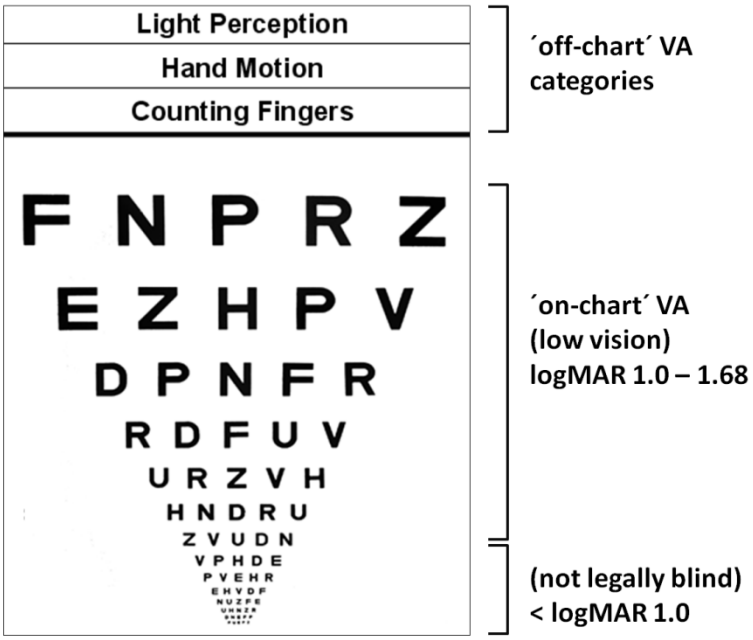
9.2.1 Primary Endpoint

- Proportion of eyes with clinically relevant recovery of VA from Baseline or in which Baseline VA better than 1.0 logMAR was maintained at Month 12, compared to matching external natural history control group

CRR of VA is defined below and illustrated in Figure 1:

- For any “off-chart” VA category (CF, HM, LP or NLP), CRR in VA is defined as the ability to read at least 5 letters “on-chart” (the equivalent of one full chart line) at the last available assessment
- For “on-chart” VA, CRR in VA is defined as the ability to read at least 10 additional letters (equivalent to two chart lines) at the last available assessment

Figure 1: VA categories



CRR from Baseline for eyes (treated independently) and for patients (with at least one eye with CRR) will be determined.

Proportion of eyes with CRR of VA from Baseline or in which Baseline VA better than 1.0 logMAR was maintained at Month 12, will be compared to a matching external natural history control group which is generated as defined below.

Data from the previously conducted Case Record Survey (CRS; SNT-IR-006) and from the newly ongoing CRS (SNT-CRS-002) will be used to generate a combined CRS control dataset which will be applied as an external natural history control group for comparison against patients treated with idebenone in this open label study. All patient VA data in the combined CRS control dataset will have VA values observed at a known time since the onset of symptoms and all VA data subsequently captured, regardless of the assessment time, will be included in the combined CRS database. This approach will be used to compare data collected in this open label study to the combined CRS idebenone naïve patients control dataset for the primary endpoint.

In order to optimize the comparability of patient data in the combined CRS control dataset to this open label study for the primary endpoint, a subgroup of patient VA data points from the CRS control dataset will be prospectively defined as follows:

1. Since there is no treatment to be considered in the combined CRS, in principle any VA observation at any time point after the onset of symptoms in any eye can be used as a Baseline for that eye. The primary outcome measure in the open label study is the VA at 12 months after Baseline. Therefore, using a “window” of ±3 months, any eye with a VA observation at any time point in the combined CRS control dataset which has a follow-up VA assessment within 12±3 months will be retained for use as a possible Baseline observation. All such possible Baseline observations and subsequent VA assessments will form the CRS control dataset subgroup to be compared to the Baseline of the open label study.
2. In the open label study, the average time from the onset of symptoms to the start of idebenone treatment will be calculated once all data is available. The start of the idebenone treatment will be used as the Baseline in the statistical analyses.
3. For each VA observation retained in the CRS control dataset subgroup, for each eye the time from the onset of symptoms at each possible Baseline time point will be calculated.

4. For each eye in the CRS control dataset subgroup, the VA observation which is closest in time since the onset of symptoms to the average time since onset of symptoms at Baseline calculated for the open label study (see 2) will be selected as the Baseline VA observation for that eye. Any eye in the CRS control dataset subgroup with a time since onset >6 months after the average time since onset at Baseline in the open label study will be discarded. The resulting data set will from the "final CRS control dataset". In this way, Baseline observations in the final CRS control dataset will be closely matched to the Baseline in the open label study.
5. The change from Baseline in VA at 12±3 months for each eye in the final CRS control dataset selected as described for the primary endpoint will be compared to the change from the Baseline visit to the visit scheduled at Month 12 in the open label study.

This algorithm will guarantee that the time from the onset of symptoms to the Baseline assessment is comparable between the final CRS control dataset and the open label study.

9.2.2 Secondary Endpoints

- Components of the primary endpoint:
  - Proportion of eyes with CRR of VA from Baseline at Month 12 compared to matching external natural history control group
  - Proportion of eyes in which Baseline VA better than 1.0 logMAR was maintained at Month 12 compared to matching external natural history control group
- Proportion of eyes in patients treated with idebenone >1 year after the onset of symptoms with CRR of VA from Baseline or in which Baseline VA better than 1.0 logMAR was maintained at Month 12 compared to external natural history control group, in all patients and classified by mutation
- Proportion of eyes and patients treated with idebenone ≤1 year after the onset of symptoms with CRR of VA from Baseline or in which Baseline visual acuity better than 1.0 logMAR was maintained following 6, 18 and 24 months of treatment with idebenone compared to matching external natural history control group, in all patients and classified by mutation
- Proportion of eyes/patients treated with idebenone ≤1 year or >1 year after the onset of symptoms with "Off-chart" VA at Baseline in whom VA improves to better than 1.60 logMAR by Month 6, 12, 18 and 24
- Proportion of eyes/patients treated with idebenone ≤1 year or >1 year after the onset of symptoms with VA in the categories of better than 1.0 logMAR, 1.0 to 1.68 logMAR and above 1.68 logMAR at each assessment time point up to Month 24
- Safety as assessed by AE count and laboratory analyses during the study

The external natural history control group for the eyes with Baseline >1 year after the onset of symptoms in the OLS will be generated as follows:

- All available eyes in the external natural history dataset will be considered, regardless of whether the eye in question was used in the control group for the primary objective or not
- All VA assessments data collected >1 year after the onset of symptoms are considered as potential baseline values
- If a potential baseline value does not have a follow-up VA assessment within 12±3 months, it will be excluded
- The remaining potential baseline values will be categorized in the following time since onset bins: between >1-2 years, >2-3 years, >3-4 years or >4-5 years
- If there are several potential baseline values for the same eye in the same bin, the eye with the baseline value closest to the midpoint of the bin will be selected

- The selected baseline value and the follow-up VA assessment within12±3 months in the same eye will be included in the external natural history control group for the eyes in the OLS with baseline >1 year after the onset of symptoms
- It should be noted that different cuts (various baseline with corresponding follow-up VA values) from the same eye can be used multiple times, both for the analysis of the primary endpoint (only once) and for the analysis of eyes with baseline >1 year after the onset of symptoms (not more than once within each of the four bins defined above)

9.2.3 Safety Variables

Safety will be assessed based on a series of parameters, including:

- Adverse events/AESIs
- Physical examinations
- Vital signs
- Clinical laboratory values (haematology, biochemistry and urine analysis)

9.3 Analysis Populations

9.3.1 Intent-To-Treat Population

The Intent-To-Treat (ITT) population will include all enrolled patients who received at least one dose of the study medication and provide at least one post-baseline VA assessment and are confirmed carriers of only one of the three major LHON mtDNA: G11778A, G3460A or T14484C.

9.3.2 Safety Population

The Safety Population will include all enrolled patients who received at least one dose of study medication.

9.4 Analysis Methods

9.4.1 Analysis of Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized with descriptive statistics.

Demographic and Baseline analysis will be performed on the Intention-To-Treat population.

9.4.2 Efficacy Evaluation

The primary analysis will be based on Intention-To-Treat principle as change from Baseline.

The primary endpoint will be analysed using a logistic regression model. The binary response will be used as the dependent variable. The independent variables include the treatment group (idebenone treated patients versus untreated control group) and mutation group (G11778A, G3460A, T14484C). The difference between the idebenone treated patients versus untreated control group will be estimated with odds ratio estimates, 95% confidence intervals and two-sided p-values.

All patients who have at least one post-baseline assessment at 12±3 months after Baseline will be included in the primary analysis. This approach is chosen due to the lack of pre-defined visit structure in the control dataset. As a sensitivity analysis, the impact of incomplete data will be assessed by analysing the primary endpoint with a generalized linear mixed model. For this purpose, the SAS GLIMMIX procedure for binomial data with logic link will be used to estimate the treatment differences. Factors similar to the ones used for the primary endpoint will be included in the model. The data from the control dataset will be classified as visits by selecting the assessment which is closest to 6, 12, 18 and 24 months from all assessments conducted within a window of ±3 months. The treatment difference at Month 12 will be estimated using contrasts.

The secondary endpoints based on counts of eyes/patients will be analysed with methods similar to the primary endpoint.

The baseline VA will be used as a covariate and treatment group and mutation as fixed factors. A mixed model for repeated measures (MMRM) will be used to assess the impact of incomplete data. The responder status (CRR or no CRR) will be used as independent variable instead of the treatment group, as this data are not available in the control dataset.

At least the following subgroups will be analysed:

- Each primary LHON mtDNA mutation separately (G11778A, G3460A, T14484C)

9.4.3 Safety Evaluation

The disposition of the patients will be summarized by tabulating the number of enrolled, completed and discontinued patients. The reasons for premature discontinuations will be tabulated. The extent of exposure will be summarized by tabulating the duration of the study treatment.

All adverse events (AEs) will be coded using the MedDRA dictionary. The treatment-emergent AEs (i.e., events which start or worsen during the study treatment) will be tabulated by system organ class and preferred term. Both subject and event counts will be calculated. In addition, the treatment-emergent AEs will be evaluated by severity and by relationship to the study treatment. The serious AEs and AEs leading to a premature discontinuation will also be summarized.

The clinical laboratory variables and vital signs will be summarized descriptively, including a tabulation of normal and abnormal values.

9.5 Analyses

The final analysis for the primary endpoint will be conducted at the time when all subjects enrolled in this open label intervention study have completed Visit 6/Month 12. The following efficacy and safety parameters will be reported:

Efficacy (primary endpoint):

Proportion of eyes in patients treated with idebenone ≤1 year after the onset of symptoms with CRR of VA from Baseline or in which Baseline VA better than 1.0 logMAR was maintained at Month 12, compared to matching external natural history control group

Safety (secondary endpoint):

The count of patients who experienced abnormal biochemistry, haematology and/or urine test results will be reported, compared to the Baseline assessments.

A detailed analysis plan will be prepared as part of the SAP prior to database lock.

Final analyses will be conducted and a Clinical Study Report prepared when the last patient has left the study.

9.6 Sample Size and Power Considerations

The present study is designed to provide sufficient statistical power for a pre-planned indirect comparison of the primary endpoint against an external natural history control group.

As defined in the original LEROS study protocol (Version1.0, 29 January 2016, Section 9.6), the sample size calculation for LEROS assumed an expected 24% responder rate in the external natural history control group (combined data from SNT-IR-006 and SNT-CRS-002). The protocol defines a pre-planned check of the estimate of responder rate in the control group, once the enrolment of the new natural history study (SNT-CRS-002) has been completed. In case the responder rate in the control group is different from 24%, a sample size re-calculation using the updated control group estimate can be considered.

As SNT-CRS-002 study was completed, the data collected in the natural history studies has now been checked for the estimate of the responder rate. Based on the combined data from 175 eyes in the two natural history studies (SNT-IR-006 and SNT-CRS-002), the estimated responder rate is below 22%, i.e. lower than the initially expected rate of 24%. Although the determination of the exact responder rate for the natural history studies requires final data from the LEROS study for matching purposes, it is reasonable to assume that the responder rate of the natural history studies is not higher than 22%. The sample size for LEROS study is therefore re-calculated using the same methods as in the original protocol (Version1.0, 29 January 2016). In order to reach a power of 90% for the comparison of the responder rates between the natural history studies (assumed to be 22% instead of 24%) and the LEROS study (assumed to be 40%, as defined in the protocol), evaluable data from altogether 110 eyes from the LEROS study is required. In order to account for a drop-out rate of 30% (as defined in the protocol), at least 80 patients (equal to 160 eyes) will be enrolled to the LEROS study.

The sample size calculation was done with nQuery Advisor version 8.3.

For the sample size for the eye treated >1 year after the onset of symptoms and the corresponding external natural history control group, the aim is to collect VA data from same number of eyes as for the primary objective in order to compare the patients treated ≤1 and >1 year since the onset of symptoms and to compare patients treated with Raxone >1 year since the onset of symptoms with the corresponding natural history control group, assuming sufficient natural history control data can be collected to generate the natural history control group as described in 9.2.2.

9.7 Quality Assurance of Data

All data collected will be entered into a validated computerised clinical data management system.

Analysis of the data will only be performed after all queries have been resolved using appropriate software for analysis.

Data management and data analysis will be performed according to a prospectively prepared plan and in compliance with the QA system of the data management and data analysis provider.

10 Ethics, Regulatory and Administrative Considerations

The study will be conducted according to the Declaration of Helsinki, Directive 2001/20/EC, Guideline for Good Clinical Practice (GCP) 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),and applicable local regulatory requirements and laws.

10.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

The IRB/IEC must be constituted according to the local laws/customs of each participating country. It is recommended that it should include:

(a) At least 5 members
(b) At least one member whose primary area of interest is in a non-scientific area
(c) At least one member who is independent of the institution/ study site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the study should vote/ provide opinion on study-related matters.

This protocol and any other documents that the IRB/IEC may need to fulfil its responsibilities, including the Patient Information and Informed Consent Form, patient recruitment procedures, and information about payments and compensation available to patients, will be provided by the Study Sponsor to the Principal Investigator, and will be submitted to the appropriate Committee

or Board by the Principal Investigator, and their written unconditional approval should be in the possession of the investigator and the sponsor before commencement of the study. Relevant Santhera Pharmaceuticals (Switzerland) Ltd. data will be supplied by the Sponsor to the hospital/university/independent IRB/IEC for the protocol's review and approval. The IRB/IEC's unconditional approval of the protocol and the written informed consent statement will be transmitted by the Sponsor. This approval must refer to the study by exact protocol title and number, and should identify the documents reviewed and state the date of review.

No deviations from, or changes to, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the patients (Urgent Safety Measure USM) or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of monitor(s), telephone number(s)). In case the investigator takes an Urgent Safety Measure, the investigator shall inform Santhera representatives as soon as possible but at least within 24 hours and ensure that IRB/IEC is informed. Such modifications will be submitted to the IRB/IEC for information only. However, written verification that the modification was submitted should be obtained. The investigator will transmit approvals/verifications to the Sponsor, in writing.

The investigator must inform the IRB/IEC of:

- all subsequent protocol amendments, informed consent changes or revisions of other documents originally submitted for review
- serious and/or unexpected AEs occurring during the study, where required
- all subsequent protocol modifications (for information)
- new information that may affect adversely the safety of the patients or the conduct of the study
- an annual update and/or request for re-approval, where required
- study completion, where required.

10.2 Authorities

The procedures laid out in 21 CFR 50, 54, 56, 312, 314 and/or local laws must be followed and all documents must be submitted to all concerned authorities before the clinical study may commence.

10.3 Patient Information and Informed Consent

The principles of informed consent in the Declaration of Helsinki must be implemented in the clinical study before any protocol-specified procedures or interventions are carried out.

Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC.

10.4 Monitoring

This trial will be managed and monitored in accordance with the ICH Guideline for Good Clinical Practice (ICH Topic E6, Integrated Addendum E6 (R2), 2016). The Quality Risk Assessment of the study is performed according to Santhera SOP050. A Clinical Trial Risk Assessment and Management Plan for this study will be developed and maintained during the study, and will define and document tasks and scope of centralized, on-site monitoring, as well as QA activities such as systems' and site audits.

It is understood that Santhera Pharmaceuticals (Switzerland) Ltd. or their representative will contact and visit the investigators regularly for monitoring purposes. The monitor will be allowed, on request, to inspect the various records of the trial (CRFs and other pertinent data, provided that patient confidentiality is maintained in accordance with local requirements). It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being

entered. The monitor should have access to laboratory test reports and other patient records needed to verify the entries on the CRF. The investigator (or her/his deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

Before any patients can be enrolled an Initiation Visit will be conducted. The investigator and the full study site staff must be available at this visit. All staff must have an Initiation Visit before they conduct any study specific procedures.

10.5 Audit and Inspection

Investigator sites, the study database and study documentation may be subject to quality assurance audits during the course of the study either by Santhera Pharmaceuticals (Switzerland) Ltd., or their appointed representatives. In addition, regulatory bodies at their discretion may conduct inspections.

10.6 Source Documents

The investigator(s)/institutions(s) will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) providing direct access to source data/documents.

The investigator shall permit the authorized sponsor, agents of the sponsor, and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held, and to inspect and copy all records relating to an investigation, including subject records. Completed CRFs must be made available for review by the sponsor, agents of the sponsor, the clinical monitor and the regulatory agencies. To ensure the accuracy of data submitted, it is mandatory that representatives of the sponsor and of the regulatory agencies have direct access to source documents (i.e., subject medical records, charts, laboratory reports, etc.). Subject confidentiality will be protected at all times.

10.7 Data Protection

Personal and sensitive personal data will be treated as confidential. The results of the study will be made available for review by authorized representatives of Santhera Pharmaceuticals (Switzerland) Ltd. and/or submitted to one or more sponsor offices worldwide, the ethics committee and regulatory authorities.

For this purpose the data may be transferred to other countries. The data collected from this study are considered as personal/sensitive data.

Prior to the subject's enrolment in the study, the subject's consent is required for the data to be used for these purposes and to gain direct access to their medical records for data verification purposes.

The subject's must be assured that their identity will be protected. To facilitate this, a unique identification code will be assigned by the investigator to each study subject. This will be used instead of the subject's name and cross referenced with the subject's date of birth (according to country regulations, at the minimum the year and at the maximum the year and month will be collected) when reporting AEs and /or other study related data.

10.8 Case Report Forms

The Case Report Form (CRF) and the protocol are both confidential. The CRF will remain the property of Santhera Pharmaceuticals (Switzerland) Ltd. at all times. Conventional NCR paper CRFs or Electronic Data Capture (EDC) will be used for this study. Appropriate information will be supplied to the centres in the CRF Completion Guidelines.

The CRFs will be supplied by Santhera Pharmaceuticals (Switzerland) Ltd. All CRFs are to be completed by the examining personnel and reviewed and signed by the investigator(s). CRFs must accurately reflect data contained in subjects' records (i.e. source documents).

10.9 Investigator Site File

At the beginning of the study, an investigator's study file will be established at the study centre. The investigator/institution is responsible for maintaining the study documents as specified in the guideline for ICH-GCP (CPMP/ICH/135/95) and as required by the applicable regulatory requirement(s). The investigator/institution must take measures to prevent accidental or premature destruction of these documents.

The following guidelines, instructions and certifications are regarded as relevant supplements and will be provided for the investigator's study file at each centre:

- IB
- The approval of the relevant ethics committees
- List of participating centres
- Instructions for completion of the CRF

10.10 Premature Termination of the Study

If the study is prematurely terminated or suspended, Santhera Pharmaceuticals (Switzerland) Ltd. will inform promptly the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/ethics committee will also be informed promptly and provided with the reason(s) for the termination or suspension by Santhera Pharmaceuticals (Switzerland) Ltd. or by the investigator/institution, as specified by the applicable regulatory requirement(s).

Potential reasons for premature termination of the study include:

- Unacceptable safety concerns of the study drug being studied and the safety of participants is no longer assured.
- The study objectives can be answered distinctly after an intermediate analysis.

The recruitment of trial participants is insufficient and the successful termination of the clinical trial does not seem to be possible.

10.11 Clinical Study Report

Santhera Pharmaceuticals (Switzerland) Ltd. or its representative will prepare a final integrated clinical/statistical report which is compliant with the ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports (ICH E3).

10.12 Patient Insurance and Indemnity

Santhera Pharmaceuticals (Switzerland) Ltd. will provide the insurance in accordance with local guidelines and requirements as a minimum for the subjects participating in this study. The terms of insurance will be kept in the study files.

10.13 Amendments to the Protocol

Modifications of the signed protocol, where substantial, are only possible by approved protocol amendments and with the agreement of all responsible persons. The procedure for approval of a protocol amendment is identical to that for approval of the protocol. The IRB/IEC must be informed of all substantial amendments and should be asked for its opinion as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented.

The investigator must not implement any deviation from, or change to the protocol, without discussion with, and agreement by Santhera Pharmaceuticals (Switzerland) Ltd. and prior review and documented approval/favourable opinion of the amendment from the relevant IRB/ethics committee, except where it is necessary to eliminate an immediate hazard to study subjects, or where the change(s) involves only logistical or administrative aspects of the study, i.e. non-substantial (e.g. change in monitor(s), change of telephone number(s)).

Protocol amendments will be submitted to the appropriate authority(ies) as required by the applicable regulatory requirement(s).

10.14 Disclosure of Information

In signing the final protocol, every participating investigator agrees to keep all information concerning the study and the investigational product confidential. The confidentiality obligation applies to all personnel involved at the investigational site.

10.15 Definition of End of Study

The end of the trial is defined as the Last Patient Last Visit date. Last Patient Last Visit is either the date of the last patient visit or the last patient to complete the study, or the date at which the last data point from the last patient, which was required for statistical analysis (i.e. key safety and efficacy results for decision making) was received, whichever occurs later.

At the end of the study, in countries where the drug, is not commercially available, every effort will be made to assure continued access to idebenone to the patients who the investigator believes derived and are still deriving a benefit from treatment administration and a continuous use is clinically indicated, according to the local specific regulation.

10.16 Publication and Presentation Policy

The results of this study will be published and/or presented at scientific meetings in a timely manner. Any formal publication of study results will be a collaborative effort between Santhera Pharmaceuticals (Switzerland) Ltd. and the investigator(s). All manuscripts or abstracts will be reviewed and approved in writing by Santhera Pharmaceuticals (Switzerland) Ltd. prior to submission.

10.17 Archiving and Data Retention

Copies of all study documents must be retained by the sponsor and investigator for a minimum of 2 years after the last marketing application has been approved or the drug is withdrawn. The sponsor will notify the investigator when documents can be destroyed. The final database will be archived by Santhera Pharmaceuticals (Switzerland) Ltd. according to regulatory requirements.

10.18 Registration of the Clinical Trial in a Publicly Accessible Database

The Sponsor has registered this clinical trial in a publicly accessible database (such as EudraCT or clinicaltrials.gov) before recruitment of the first subject, in compliance with the Declaration of Helsinki.

ClinicalTrials.gov Identifier: NCT02774005.

11 References

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