[redacted]

EU Risk Management Plan for Raxone® (idebenone)

RMP version to be assessed as part of this application:

RMP Version number:	1.18
Data lock point for this RMP:	20 Dec 2021
Date of final sign-off:	28 July 2022
Rational for submitting an updated RMP:	Closing Sequence of procedures EMEA/H/C/003834/S/0029 and EMEA/H/C/003834/II/0031
Summary of significant changes in this RMP:	Consolidated RMP (RMP v1.15 related to procedure EMEA/H/C/003834/S/0029 merged with RMP version 1.17 related to procedure EMEA/H/C/003834/II/0031)
Other RMP versions under evaluation:	None
QPPV name:	[redacted]
QPPV signature:	[redacted]

Table of content

LIST OF ABBREVIATIONS

AE	Adverse Event
ADR	Adverse Drug Reaction
ALT	Alanine Transaminase
ASA	Active Systemic Anaphylaxis
ATC	Anatomical Therapeutic Chemical
AOA	Ataxia with oculomotor apraxia
AST	Aspartate Transaminase
ATP	Adenosine Triphosphate
BL	Baseline
C_{max}	Maximum concentration
CCSI	Company Core Safety Information
CI	Confidence Interval
CYP	Cytochrome P450
DMD	Duchenne Muscular Dystrophy
DSUR	Development Safety Update Report
EC	European Commission
ECG	Electrocardiogram
EAP	Expanded Access Programme
EEA	European Economic Area
EMA	European Medicines Agency
EOT	End of Treatment
EPAR	European Public Assessment Report
EU	European Union
FRDA	Friedreich's Ataxia
GDPR	General Data Protection Regulation
GGT	Gamma-glutamyl Transferase
hERG	Human Ether-à-go-go-Related Gene
IC	Inhibitory Concentration
ICARS	International Cooperative Ataxia Rating Scale
Idebenone/Raxone	Terminology used for NICOSIA and MICONOS studies which included both a low dose of 180/360 mg t.i.d. idebenone (i.e. not Raxone150 mg tablets) and Raxone150 mg tablets
IONIA	Idebenone effects On Neurological ICARS Assessments
INN	International Nonproprietary Name
kg	Kilogram
LD	Lethal Dose
LHON	Leber's Hereditary Optic Neuropathy
LogMAR	Logarithm of the Minimum Angle of Resolution
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MDR-MDCK	Multidrug-resistant Madin Darby Canine Kidney
MELAS	Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like episodes
mg	Milligram
MICONOS	Mitochondrial protection with Idebenone in Cardiac Or Neurological Outcome Study
ml	Millilitre

µM	Micromolar
MS	Multiple Sclerosis
mtDNA	Mitochondrial deoxyribonucleic acid
NADH	Nicotinamide adenine dinucleotide
ng	Nanogram
NICOSIA	NIH Collaboration with Santhera In Ataxia
NINDS	National Institute of Neurological Disorders and Stroke
NOAEL	No Observed Adverse Effect Level
OFU	Open Follow Up
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report
P-gp	P-glycoprotein
PK	Pharmacokinetic
PIL	Patient Information Leaflet
PPMS	Primary Progressive Multiple Sclerosis
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV/PhV	Pharmacovigilance
QPPV	Qualified Person for Pharmacovigilance
RHODOS	Rescue of Hereditary Optic Disease Outpatient Study
RMP	Risk Management Plan
SAE	Serious Adverse Event
SCA	Spino-cerebellar Ataxia
SD	Standard deviation
SmPC	Summary of Product Characteristics
SNT	Santhera
SOC	System Organ Class
tid	three times daily
ULN	Upper Limit Normal

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Idebenone
Pharmacotherapeutic group(s) (ATC Code)	ATC Code: N06BX13
Marketing Authorisation Applicant	Santhera Pharmaceuticals (Deutschland) GmbH Marie-Curie-Strasse 8, 79539 Lörrach, Germany
Medicinal products to which this RMP refers	Idebenone
Invented name(s) in the European Economic Area (EEA)	Raxone®
Marketing authorisation procedure	Centralised procedure Hybrid application: Article 10(3) of Directive 2001/83/EC
Brief description of the product	Chemical class Idebenone (2, 3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1, 4-benzoquinone) is a short chain benzoquinone capable of transferring electrons directly onto complex III of the mitochondrial electron transport chain, thereby circumventing complex I and restoring cellular energy levels under experimental conditions of complex I deficiency *in vitro* and *in vivo*.
	Summary of mode of action In Leber's Hereditary Optic Neuropathy (LHON), idebenone can bypass complex I of the electron transport chain, which is affected by all three primary mitochondrial deoxyribonucleic acid (mt-DNA) mutations causing LHON, thereby restoring electron flux and cellular energy (Adenosine Triphosphate (ATP)) generation.
	Important information about its composition 1 film-coated tablet contains: [redacted]

[redacted]

	[redacted]
Hyperlink to the Product Information	https://www.ema.europa.eu/en/documents/product-information/raxone-epar-product-information_en.pdf
Indication(s) in the EEA	Raxone is indicated for the treatment of visual impairment in adolescent and adult patients with Leber's Hereditary Optic Neuropathy (LHON)
Dosage in the EEA	The recommended dose is 900 mg/day idebenone (300 mg, three times a day). Treatment should be initiated and supervised by a physician with experience in LHON. Data regarding continuous treatment with idebenone for up to 24 months are available as part of a Natural History controlled open label clinical trial.
Pharmaceutical form(s) and strengths	Film-coated tablets 150 mg Orange, round, biconvex film coated tablet of 10 mm diameter, engraved with Santhera logo on one side and '150' on the other side.

[redacted]

Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Leber's Hereditary Optic Neuropathy (LHON) is a rare disease caused by mtDNA mutations. The great majority of LHON patients harbour one of three pathogenic mtDNA mutations (G11778A, G3460A and T14484C) which affect complex I (nicotinamide adenine dinucleotide (NADH)-ubiquinone oxidoreductase) subunits of the mitochondrial respiratory chain, resulting in a defect of ATP synthesis accompanied by increased production of oxygen free radicals and causing retinal ganglion cell dysfunction and apoptosis (Tonska et al., 2010). LHON usually results in an irreversible loss of visual acuity and blindness. The natural history of LHON suggests that the great majority of patients develop bilateral disease within a few months of the first onset of symptoms after which period the deterioration in visual function stabilizes (Newman et al., 2005). Ninety-seven percent of patients have bilateral involvement within 1 year of the initial onset of symptoms (Fraser et al., 2010). In most patients with LHON, visual loss remains profound and permanent. However, spontaneous recovery of vision has been reported and found to be particularly associated with the T14484C mt-DNA mutation (37-65% chance of recovery (Nikoskelainen et al., 1996, Riordan-Eva et al., 1995) versus 4% for the G11778A mutation (Stone et al., 1992). Recovery of vision may occur years after visual deterioration (Newman et al., 1991, Stone et al. 1992) although patients in whom vision improves most substantially appear to have had recent onset of symptoms (Carelli et al., 2011). Recurrences of visual failure are extremely rare among patients both with and without visual recovery (Newman. 2005).

Incidence: The intended use of Raxone is for patients who have developed visual failure due to LHON. Patients with LHON do not have a reduced life expectancy but the likelihood of benefit of treatment with Raxone started more than 5 years after visual failure is low. The target population is therefore LHON patients with visual failure of up to 5 years duration.
There is no published information on the incidence of this condition. However, by assuming that a patient may on average live for 30 years following onset and that the prevalence estimates are constant, the general incidence rates for LHON in Europe based on a prevalence of 2.2/100,000 would be 0.08/100,000 person-years. This may overestimate the target population because published data on LHON is generally reported from disease "hot-spots" which may occur due to the genetically-inherited nature of LHON. The prevalence outside the hot-spots is generally much lower than within.

Prevalence: According to an epidemiological meta-analysis of published data (Mascialino et al., 2012) the overall prevalence of LHON in Europe is estimated to be 2.2 per 100,000 for all combined mtDNA mutations. According to EU Orphanet, the prevalence is 2/100,000.

Demographics of the target population – age, sex, race/ethnic origin.

Gender: LHON is more prevalent in males; the proportion of LHON patients that are male ranges from 72% to 83% (Jia et al., 2006, Man et al., 2003, Phasukkijwatana et al., 2006, Spruijt et al., 2006).

Age at onset: Although the disorder can develop at any time between childhood and old-age, LHON typically presents in young adult males with a median age of onset of 24 years (Nikoskelainen et al. 1996). There is no information on the age structure of the current prevalent LHON population.

Risk factors for the disease: LHON is a maternally inherited disease and is associated with mt-DNA mutation. No additional risk factors have been reported.

Main treatment options: Currently there are no treatment options available for this condition.

Mortality and morbidity (natural history): No data on mortality associated with this condition was found in the medical literature using the search terms "mortality" and "death". LHON is therefore unlikely to be associated with decreased life expectancy. However, there may be increased mortality for those patients who develop the Multiple Sclerosis-like (MS-like) illness that has been associated with LHON. This subgroup represent about 5% of all LHON patients and their estimated life expectancy is 10 years less than the general population (Bronnum-Hansen et al., 2004).

Concomitant medication(s) in the target population: As there is currently no established treatment for LHON, there is no expected concomitant medication associated with LHON itself. However, there are co-morbidities associated with LHON and medications may be required as treatment for these conditions. Supportive treatment for neurological symptoms or multiple sclerosis may span a broad spectrum of medications including those to treat pain, spasticity, constipation, bladder dysfunction, tremor, fatigue and depression. Specific treatments including GCs and interferon may also be appropriate. In the Rescue of Hereditary Optic Disease Outpatient Study (RHODOS) study, concomitant medications were unremarkable. The most common concomitant medications were simple analgesics, anti-inflammatory agents and antibiotics.

Important co-morbidities found in the target population:

Multiple Sclerosis like illness: A disease clinically similar to multiple sclerosis (MS-like) has been reported for LHON. The MS-like condition has been reported to have a prevalence of 5% in the LHON population and is 50 times greater than in the general population (Palace et al., 2009).

Mental Retardation: The prevalence of this condition among LHON patients has been reported to be between 3% and 13% (Fazzi et al., 2003).

Additional neurologic symptoms: Spastic atonia, ataxia, juvenile onset encephalopathy, and peripheral neuropathy have been rarely reported as additional neurologic symptoms/syndromes in LHON patients (Yu-Wai-Man et al., 2011).

Cardiac disease: Patients with LHON frequently experience electrocardiogram (ECG) abnormalities, including heart rhythm abnormalities, disturbances of atrioventricular and/or ventricular conduction, shortening of the PR-interval with or without delta wave (Wolff-Parkinson-White syndrome), widening of the QRS-complex and prolongation of QTc (Bower et al., 1992, Nikoskelainen et al., 1994, Ortiz et al., 1992, Sorajja et al., 2003).

Concomitant medication(s): As there is currently no established treatment for LHON, there is no expected concomitant medication associated with LHON itself. However, there are co-morbidities associated with LHON and medications may be required as treatment for these conditions.

Supportive treatment for neurological symptoms or multiple sclerosis may span a broad spectrum of medications including those to treat pain, spasticity, constipation, bladder dysfunction, tremor, fatigue and depression. Specific treatments including corticosteroids and interferon may also be appropriate.

In the Rescue of Hereditary Optic Disease Outpatient Study (RHODOS) study, concomitant medications were unremarkable. The most common concomitant medications were simple analgesics, anti-inflammatory agents and antibiotics.

Part II: Module SII - Non-clinical part of the safety specification

Key Safety findings (from non- clinical studies)	Relevance to human usage
Toxicity	
Single and repeat-dose toxicity Single and repeat dose toxicity studies were unremarkable and revealed only species specific changes.	The Lethal Dose $(LD)_{50}$ observed in single dose toxicity studies in both mouse and rat corresponds to a human equivalent dose at least 50 times higher than the recommended dose in humans. Single and repeat dose toxicity studies have not revealed any important safety concern for human use.
Reproductive and developmental toxicity In the rat fertility and early embryonic development study and in embryo-foetal developmental studies in rats and rabbits there was no evidence of embryotoxic or teratogenic effects or significant maternal toxicity (Ihara et al., 1985b, 1985c, 1985d, EMEA/387246/2009).	The data suggest that idebenone has no effects on fertility and general reproductive performance and there is no evidence of embryotoxic or teratogenic effects. However, as the safety of idebenone in pregnant women has not been established, idebenone should only be administered to pregnant women or women of child-bearing age likely to become pregnant if it is considered that the benefit of the therapeutic effect outweighs any potential risk.
Genotoxicity No mutagenic or clastogenic risk has been shown to be associated with idebenone.	No important safety concern identified.
Carcinogenicity In dietary carcinogenicity studies, mice and rats were treated with idebenone for 24 months at dose levels of 0, 640, 1280, 2000 mg/kg/day in mice, and 0, 500 and 1000 mg/kg/day in rats. No treatment-related tumour response was observed. A low incidence of squamous and basal cell tumours was seen only at the highest dose (1000 mg/kg/day) in the forestomach of female rats. It was agreed that these proliferative findings in the forestomach, a rodent-specific organ, were most likely a consequence of local	Overall, there is no evidence that to suggest that idebenone is a carcinogen. No important safety concern identified.

irritation, and were considered to be of low clinical relevance (EMEA/387246/2009).	
Immunotoxicity Idebenone does not seem to be an immunotoxic compound neither in the repeat dose toxicity studies nor when idebenone was examined by means of the antibody production test in Ta:A/J mice and the active systemic anaphylaxis (ASA) test in guinea-pigs (EMEA/387246/2009).	No important safety concern identified.
General safety pharmacology	
Cardiovascular (including potential for QT interval prolongation) In the *in vitro* Human Ether-à-go-go-Related Gene (hERG) assay (RCC A07143), the IC_{50} and IC_{20} concentrations were approximately 95 and 9 times higher than the mean maximum idebenone concentration in human plasma following repeat dosing of 750 mg tid (C_{max} =19.2 ng/ml; SNT-I-003), a dose which is above the current intended clinical dose of 300 mg tid. No adverse cardiovascular effects were noted in a 39-week repeated-dose toxicity study in dogs (Harlan C32393; Module 2.6.6.3). The mean C_{max} concentrations in dog plasma at the high dose of 1000 mg/kg/day (above the no observed adverse effect level (NOAEL) of 750 mg/kg/day) were between 254 ng/ml and 2271 ng/ml, which was approximately 13 – 118-fold higher than when compared with the highest mean C_{max} values in humans at 750 mg tid (C_{max} =19.2 ng/ml; SNT-I-003).	The non-clinical data supports the ECG data obtained from a number of clinical Phase I studies, where both single or repeated (t.i.d) doses of idebenone 750 mg, (higher than the dose intended for use in LHON patients), had no effect on ECG morphology or the QTc interval in human volunteers (studies SNT-I-001 and SNT-I-003; see Module 2.7.2) and single doses of idebenone up to 1050 mg administered in human volunteers had no effect on the ECG as seen in routine ECG assessments (SNT-I-004; see Module 2.7.2). In Phase III Studies in LHON patients (300 mg tid, SNT-IR-004) or Friedreich's Ataxia (FRDA) patients (up to 750 mg tid, SNT-IR-001) there was also no evidence of an influence of idebenone treatment on QT, QTcB or QTcF values in patients treated for periods of up to 1 year. Taken together the *in vitro* and *in vivo* safety data in animals demonstrate no overt cardiovascular safety concerns with respect to the clinical use of idebenone. No important safety concern identified.
Nervous system Idebenone did not exhibit any adverse neurological effects.	Idebenone has little effect on either the central nervous system or somatic nervous systems. No important safety concern identified.
Mechanisms for drug interactions The cytochrome P450 inhibition studies suggest that idebenone and QS10 are likely to display	A drug-drug interaction study was conducted in 32 healthy volunteers and indicate that on the first

weak to moderate inhibition in vitro at the major Cytochrome P450 (CYP) isoforms tested as the IC50 values ranged from 1.69 µM for idebenone on the CYP2B6 isoform up to 17.1 µM for QS10 on the CYP1A isoform. However, these concentrations are far above the expected human in vivo plasma concentrations. In order to assess the magnitude of interactions, subsequent investigations were carried out in more detailed Ki inhibition assays to determine the affinity of the compounds for the CYP isoforms. These data were used in conjunction with the maximum plasma concentrations observed in vivo to calculate the magnitude of a potential interaction. The magnitude of interactions for idebenone and QS10 were calculated using the recommendations of the European Medicines Agency (EMA). Using this guidance, the data suggest that there would be minimal, if any interaction observed in vivo. In the induction studies in human isolated hepatocytes from three individual donors, both idebenone and QS10 were considered unlikely to cause significant induction of the CYP3A4, CYP2B6 or CYP1A isoforms. An in vitro study to investigate the P-glycoprotein (P-gp) liability of idebenone (CYP0104_R78) was performed in human isolated hepatocytes and demonstrated that idebenone is not a substrate of P-gp at any of the 4 concentrations tested. Idebenone was also assessed in vitro for its potential to inhibit the efflux activity of the established P-gp substrate loperamide in Multidrug-resistant Madin Darby Canine Kidney (MDR1-MDCK) cells. The data suggest that due to the low solubility of idebenone in the gastrointestinal tract it is unlikely that concentrations are reached to cause a transporter-mediated drug-drug interaction in vivo and that co-administration of idebenone with. No safety concern was identified for the co-administration of P-gp substrates.	day of oral administration of 300 mg idebenone t.i.d., the metabolism of midazolam, a CYP3A4 substrate, was not modified when both drugs were administered together. After repeated administration Cmax and AUC of midazolam were increased by 28% and 34%, respectively, when midazolam was administered in combination with 300 mg idebenone t.i.d. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving idebenone. Caution is advised and combination with these medicinal products should if possible be avoided. The warning is included in the SmPC in section 4.5. There is likely no relevant interaction between idebenone/QS10 and oral contraceptives, given the absence of induction of CYP3A4 in vitro by idebenone/QS10. The SmPC reflects the fact that idebenone is unlikely to inhibit P-gp.

Part II: Module SIII - Clinical trial exposure

Raxone has been investigated by Santhera as a sponsor for the indications of LHON which is the focus of this RMP, and also in FRDA. Data from the FRDA studies are presented for safety purposes only.

LHON indication

A total of 198 patients received treatment with Raxone and were included in the Safety Population. The mean duration of treatment in the Safety Population was 589.17 days (range: 1 – 806 days), which was equivalent to a total exposure of 319.39 person-years. A total of 154 (77.8%) of the patients undertook treatment for >12 months. A total of 149 (75.3%) patients underwent treatment at the >18-month timeframe; at the >24-month timeframe, this was 106 (53.5%).

The exposure data concerning LHON patients treated with Raxone are shown in SIII.1 below.

RHODOS

RHODOS a double-blind, randomised, placebo-controlled study (Rescue of Hereditary Optic Disease Outpatient Study, SNT-II-003) explored the efficacy, safety and tolerability of Raxone in the treatment of patients with LHON. The primary objective was to determine whether the administration of Raxone can improve visual function in LHON patients, the primary endpoint being the best recovery of Logarithm of the Minimum Angle of Resolution (logMAR) visual acuity between Baseline (BL) and Week 24 in either the right or left eye.

The study included a total of 85 subjects, 55 randomised to treatment with Raxone and 30 to placebo. The exposure data concerning patients on Raxone are shown in below.

RHODOS-Observational Follow Up (OFU) (SNT-II-003-OFU), a single visit, observational follow-up study of Patients with LHON following participation in RHODOS (SNT-II-003) has been completed. The primary objective was to assess the current logMAR visual acuity of LHON patients who participated in RHODOS trial and to compare this to their logMAR visual acuity at Visit 2/BL and Visit 5/Week 24 or last treatment visit. The study included a total of 60 subjects.

LEROS

LEROS (SNT-IV-005) is an External Natural History Controlled, Open-Label Intervention Study to Assess the Efficacy and Safety of Long-Term Treatment with Raxone in LHON.

In LEROS; a total of 199 LHON patients were enrolled in this open label study and 198 exposed to Raxone. Over half (112 [56.6%]) had the G11778A mutation, whereas 34 (17.2%) had the T14484C mutation and 35 (17.7%) had the G3460A mutation. The mean age at Baseline (BL) was 34.2 years were enrolled. Patients received 900 mg/day Raxone for a period of 24 months. Raxone was given as 3 doses of 300 mg daily, each with meals.

The primary endpoint in LEROS was the proportion of eyes that achieved a Clinically Relevant Benefit (CRB) (that is, in which there was either a Clinically Relevant Recovery [CRR] of VA from Baseline or a Clinically Relevant Stabilization [CRS]) at Month 12 in those patients that started treatment with Raxone ≤1 year after the onset of symptoms, compared to eyes of patient from an external NH control group. CRB was observed in 42.3% of eyes from LEROS patients, in contrast to 20.7% of eyes from Natural History (NH) patients. Clinically, this represents a highly relevant 104% relative improvement compared to spontaneous CRB that may occur in the control NH eyes. The estimated difference between treatment and control was statistically significant (p-value 0.0020) in favour of Raxone presenting an Odds Ratio (OR) of 2.286 (95% confidence limits 1.352, 3.884).

FRDA indication

A large clinical development program was undertaken to investigate the use of idebenone in the treatment of patients with FRDA. Three double-blind studies (Phase II NIH Collaboration with Santhera

In Ataxia (NICOSIA), Phase III Mitochondrial protection with Idebenone in Cardiac Or Neurological Outcome Study (MICONOS) and Idebenone effects On Neurological ICARS Assessments (IONIA)) have been completed so far, as well as the open-label extension of the IONIA study (IONIA extension), and the open-label extension of the MICONOS study (MICONOS extension). These studies enrolled over 300 patients with FRDA and contribute important information on idebenone safety.

The NICOSIA study was a 6-month, double-blind, placebo-controlled, phase II clinical study sponsored by the National Institute of Neurological Disorders and Stroke (NINDS), exploring the efficacy and safety of Raxone in patients with FRDA. The primary objective was to determine the effect of varying doses of Raxone on oxidative stress as reflected by the percent change from BL in the level of the oxidative stress marker 8-hydroxy-2-deoxyguanosine.

The NICOSIA study was complemented by two randomised, double-blind, placebo-controlled, phase III studies sponsored by Santhera (MICONOS and IONIA), to investigate the efficacy, safety and tolerability of Raxone in the treatment of FRDA patients. The primary objective of the MICONOS study was to compare the efficacy of Raxone treatment (three different doses administered for 12 months) with that of placebo on neurological impairment as assessed by the International Cooperative Ataxia Rating Scale (ICARS). Similarly, the primary objective of the IONIA study was to explore the efficacy of two different doses of Raxone (6-month treatment) versus placebo on neurological impairment as assessed by ICARS. For both studies, the primary endpoint was the absolute change in ICARS scores from BL assessment to treatment completion (Week 52 for MICONOS and Week 24 for IONIA). Patients completing these studies were invited to enrol in their respective open extensions: the MICONOS extension followed 200 subjects treated with Raxone for up to 2 years, whilst the IONIA extension investigated the effects of 1-year treatment with Raxone in 68 patients.

The exposure data concerning FRDA patients treated with Raxone are shown below.

Table SIII.1 : Dose and Duration of exposure (by indication)

Indication: LHON (All patients received a dose of 900 mg/day) **RHODOS**	
Duration of exposure (at least)	**Patients N (%)**
< 4 weeks	0
4-11 weeks	55 (100.0)
12-23 weeks	54 (98.2)
24 weeks	51 (92.7%)
Total patient days: 10,560	
Mean (Standard Deviation SD): 192.0 (36.1) days	
Range of exposure : 28-225 days	
Indication: LHON (All patients received a dose of 900 mg/day) **LEROS**	
Duration of exposure (at least)	**Patients N (%)**
>12 months	154 (77.8%)
>18-month	149 (75.3%)
>24-month	106 (53.5%)

Total patient days: 589.17			
Range of exposure : 1 – 806 days			
Indication: FRDA			
Dose group	**Duration of exposure**	**Patients N (%)**	**Patient days**
NICOSIA			
180/360 mg/day	Mean (SD): 181.1 (5.3) days Range: 171-191 days	12 (32.4)	2,173
450/900 mg/day	Mean (SD): 180.9 (3.5) days Range: 175-188 days	13 (35.1)	2,352
1350/2250 mg/day	Mean (SD): 183.1 (3.8) days Range: 179-192 days	12 (32.4)	2,197
Total		37 (100.0)	6,722
MICONOS			
180/360 mg/day	Mean (SD): 349.4 (62.4) days Range: 84-405 days	57 (32.9)	19,916
450/900 mg/day	Mean (SD): 356.1 (52.8) days Range: 117-466 days	57 (32.9)	20,298
1350/2250 mg/day	Mean (SD): 363.9 (22.9) days Range: 210-400 days	59 (34.1)	21,470
Total		173 (100.0)	61,684
IONIA			
450/900 mg/day	Mean (SD): 168.8 (3.66) days Range: 162-176 days	22 (47.8)	3,174
1350/2250 mg/day	Mean (SD): 169.6 (3.46) days Range: 163-176 days	24 (52.2)	4,070
Total		46 (100.0)	7,244
IONIA extension			
1350/2250 mg/day	Mean (SD): 338.5 (78.9) days Range: 33-382 days	68 (100.0) (22 patients had not been exposed to idebenone in the IONIA trial)	23,018
MICONOS extension			
1350/2250 mg/day	Mean : 629.6 days Range: 0-923 days	200 (100.0) (51 patients had not been exposed to idebenone in the MICONOS trial)	125,920

Table SIII.2: By age group (by indication)

Indication: LHON		
RHODOS		
Age group	**Patients N (%)**	
	F	M
14-17	1 (1.8)	5 (9.1)
18-29	3 (5.5)	18 (32.7)
30-44	0	13 (23.6)
45-59	3 (5.5)	8 (14.5)
≥ 60	1 (1.8)	3 (5.5)
Total	8 (14.5)	47 (85.5)
LEROS		
Age at baseline	**Patients N:** 198	
Mean (SD ; SE)	34.17 (15.177 ; 1.079)	
Median (Q1 – Q3)	32.09 (22.19 – 44.67)	
Min – Max	12.13 – 79.23	

Indication: FRDA		
Study	**Age group**	**Patients N (%)**
NICOSIA	≤ 12	8 (21.6)
	> 12	29 (78.4)
	Total	37 (100.0)
MICONOS	0–17	26 (15.0)
	18-25	48 (27.7)
	26-35	39 (22.5)
	36-45	34 (19.7)
	>45	26 (15.0)
	Total	173 (100.0)
IONIA	450/900 mg/day group Mean (SD): 13.9 (2.5) Range: 9.7-17.3 1350/2250 mg/day group Mean (SD): 13.4 (3.0) Range: 8.0-18.0	22 (47.8) 24 (52.2)
	Total	46 (100.0)
IONIA extension	Mean (SD): 13.5 (2.7) Range: 8.0-18.0	68 (100.0)
MICONOS extension	Mean (SD): 31.2 (13.7) Range: 9.0-71.0	200 (100.0)

Table SIII.3: By gender (by indication)

Indication	Study	N Patients (%)	
		F	M
LHON	RHODOS	8 (14.5)	47 (85.5)
	LEROS	52 (26.3%)	146 (73.7%)
FRDA	NICOSIA	18 (48.6)	19 (51.4)
	MICONOS	75 (43.4)	98 (56.6)
	IONIA	21 (45.7)	25 (54.3)
	IONIA extension	36 (52.9)	32 (47.1)
	MICONOS extension	64 (46)	75 (54)

Table SIII.4: By ethnic or racial origin (by indication)

RHODOS	
Ethnic/racial origin	**Patients N (%)**
Caucasian/white	53 (96.4)
Black	1 (1.8)
Other	1 (1.8)
Total	55 (100.0)
LEROS	
Ethnic/racial origin	**Patients N (%)**
American Indian or Alaska Native	2 (1.0)
Asian Indian	1 (0.5)
Black or African American	9 (4.5)
Chinese	1 (0.5)
Filipino	1 (0.5)
Caucasian/white	54 (27.3)
Other*	130 (65.7)
Total	198(100.0)

*In line with the EU GDPR 'ethnic/race' data was not collected in the eCRF for EU patients.

Data on exposure by race were not available for the FRDA indication as this condition affects primarily Caucasians and is very rare or absent among other ethnicities.

LHON Expanded Access Programme

The following information is not taken from clinical trials, but the Applicant considers the data from this programme to be relevant in the Risk Management Plan in order to support the knowledge of exposure and safety to idebenone in patients with LHON.

Santhera has established an Expanded Access Programme (EAP) late 2011 to respond to unsolicited requests from physicians seeking idebenone for patients with LHON typically presenting for treatment within 12 months of the onset of visual loss in the second eye.

Upon request Santhera encouraged the treating physician to consider a starting dose of idebenone of 900 mg/day. For this, two 150 mg idebenone tablets were to be administered orally t.i.d. with food. However, it was at the discretion of the treating physician to recommend a change in daily dose (i.e.

lower or high than 900 mg/day). Treating physicians were advised not to recommend daily treatment doses of more than 2250 mg/day due to inexistent safety data above this dose.

The EAP included an organised data collection system so that efficacy and safety data could be collected during the patient's participation in the programme.

The program started on 27 November 2011 and was completed as of 8 September 2019. A total of 111 patients were enrolled.

The Safety Population (SP) (N=111) included any patient that had received at least one dose of idebenone.

The LHON population (LHONP) (N=105) comprised patients with at least one post-Baseline VA assessment, independently of the time to onset and type of LHON-causative mtDNA mutations.

The Efficacy Population (EP) (N=87) comprised LHONP patients, with a confirmation of any one of the three major LHON-causative mtDNA mutations, with onset of vision loss in the most recently affected eye less than 12 months prior to the date of the Baseline visit and at least one post Baseline VA assessment.

For the 105 patients in LHONP and 87 patients in the EP the mean treatment duration was 25.8 months for the LHONP and 25.6 months for the EP (ranging from 2.4 to 70.4 months).

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
History of hypersensitivity reaction to idebenone or coenzyme Q10	Contraindication to avoid hypersensitivity reactions in the interests of patient safety.	No	This will remain a contraindication in the interests of patient safety.
Moderate or severe hepatic impairment or severe renal impairment.	Adopted as exclusion criteria to meet the medical standards applied to studies.	Yes	Section 4.2 and 4.4 of the SmPC will inform prescribers that patients with hepatic and renal impairment have not been investigated and that caution is advised in treatment of patients with hepatic or renal impairment.
Clinically significant abnormalities of clinical haematology or biochemistry	Adopted as exclusion criteria to meet the medical standards applied to studies.	No	There is no signal from the known metabolism of Raxone to consider this to be a contraindication.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Pregnancy or lactation	Adopted as exclusion criteria to meet the medical standards applied to studies.	Yes	-
Recent treatment with idebenone or Coenzyme Q10. Drug abuse. Participation in another clinical study within 3 months of baseline.	Adopted as exclusion criteria in order to allow for adequate evaluation of primary and secondary endpoints.	No	These exclusion criteria are not likely to have safety implications for the target population when idebenone is used in these patients.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect pre-authorisation certain kinds of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, and adverse events caused by prolonged or cumulative exposure. PAROS is a long-term PASS post authorisation obligation to collect additional safety data during long term use. Enrolment in this observational study has been completed and the clinical study database has been locked. The clinical study report has been released on 20 December 2021. LEROS is a long-term PAES post authorisation obligation on which the data are being introduced in the RMP. The primary objective of this study was on efficacy but the study provides also-long term safety data.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not included in clinical trial development plan

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Children below 14 years of age with LHON	Limited data available. Considered Missing Information
Elderly patients	Limited data available. Considered Missing Information
Patients with hepatic impairment	Not included in the clinical development programme

Type of special population	**Exposure**
Patients with renal impairment	Not included in the clinical development programme
Patients with cardiovascular impairment	Not included in the clinical development programme
Immunocompromised patients	Not included in the clinical development programme
Patients with other relevant co-morbidity	Not included in the clinical development programme
Population with relevant different ethnic origin	In the conducted studies, most of the patients were Caucasian (96.3%). There is no reason to consider that the safety profile of idebenone would differ in other races.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Idebenone has been in use for the treatment of cerebrovascular diseases since its approval in Japan in 1986 (Marketing Authorisation Holder, MAH: Takeda, International Birth Date: 30 September 1986). Since then, Takeda has been granted a marketing authorisation for the treatment of cognitive disorders in Portugal, Argentina, Italy and Mexico.

In the European Union (EU), Santhera received on 08-Sep-2015, a Marketing Authorisation (MA) under exceptional circumstances for Raxone® (idebenone 150 mg film-coated tablets) for the treatment of visual impairment in adolescent and adult patients with LHON. In addition, on 22-Aug-2017, an MA for Raxone® in the LHON indication was granted in Israel. The recommended dose is 900 mg/day (300 mg, three times a day). Raxone® received an MA under exceptional circumstances in the LHON indication in Serbia (22-Jan-2019). Raxone® also received an MA in South Korea on 10-Sep-2019.

A Marketing Authorisation Application (MAA) for idebenone in the EU for the Duchenne Muscular Dystrophy (DMD) indication was submitted to the EMA on 25-May-2019 under the trade name Puldysa®. This application was withdrawn on 28 October 2020 and the corresponding clinical development program stopped, including the early access schemes.

Santhera marketed idebenone in Canada for the symptomatic management of patients with FRDA under the trade name Catena® between Oct-2008 and 30-Apr-2013.

SV.1.1 Method to calculate exposure

The post-authorisation exposure for patients taking Raxone® have been calculated with the Standard Assumptions as follows:

- All patients used the recommended daily dose of 900 mg, i.e. 3x2 tablets of 150 mg; although in rare cases dosing was modified by the treating physician.
- The treatment is chronic and there is no indication that there would be significant systematic patient non-compliance with the treatment as prescribed.
- There is no systematic off-label use of the product that is sold via the normal commercial distribution channels and exposure of patients in non-approved indications can be tracked separately.
- 'Sales volume' can be stated as total number of tablets distributed, regardless of whether supply was charged or free of charge.
- Regular repeat orders for the same patient will occur during the reporting period, because of the price of the product the wholesalers and pharmacies will limit stock levels and patients will keep only a very limited number of packages at their home and in most cases only the one they are using.

Based on these assumptions, the following formula was used to calculate interval patient exposure:

Estimated number of patients exposed = Number of tablets sold / (6 tablets x 365 days)

The post authorisation exposure for patients with cognitive disorders taking Catena® has been calculated by taking the total amount of tablets sold and assuming that three tablets irrespective of strength were taken daily for the whole treatment period.

SV.1.2 Exposure

In Canada, Santhera was granted conditional approval for idebenone (same product as Raxone, marketed under the brand name Catena) in the symptomatic management of patients with FRDA from July 2008 until April 2013. In Canada, 137 patients received therapy with CATENA® between Oct-2008 and Apr-2013. Since the launch of idebenone (Raxone®) in Oct-2015 up to 08.Sep.2021, a total of 5,592,960 tablets of Raxone® have been sold. Therefore, it is estimated that 2,554 patients were exposed to Raxone® through commercial supply (free-of-charge supply not included).

The last PSUR of Takeda Pharmaceuticals for idebenone that is available to Santhera (DLP 30-Sep-2017), assuming an average daily dose (ADD) of 135 mg, the patient exposure to idebenone from marketing experience was estimated to be 1,467,5 million ADDs, corresponding to approximately 4,021,709 patient-years of treatment, cumulatively. The most recent Takeda PSUR had its DLP on 30-Sep-2020 was submitted to the concerned authorities by Takeda in December 2020 (3-year reporting interval PSUR) but is not available to Santhera.

No systematically collected information is available for post authorisation exposure by age, gender or dose.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

There is no physical incentive for the patient to ingest a higher dose than prescribed by his physician. Mood-changing properties, reward mechanisms and drug-seeking behaviour are neither expected to occur in this pharmacological class, nor have they been observed; so, idebenone cannot be considered to have addictive potential.

Due to the generally good tolerability and innocuous nature of idebenone, there is no incentive for those with self-harm or suicidal ideation.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

System Organ Class	Risk	Assessment
Gastrointestinal disorders	Diarrhoea	The clinical impact of these risks on patients is considered minimal in relation to the severity of the indication treated
	Nausea, vomiting, anorexia, dyspepsia	The clinical impact of these risks on patients is considered minimal in relation to the severity of the indication treated
Skin and subcutaneous tissue disorders	Rash, pruritus	The clinical impact of these risks on patients is considered minimal in relation to the severity of the indication treated
Musculoskeletal and connective tissue disorders	Pain in extremity	The clinical impact of these risks on patients is considered minimal in relation to the severity of the indication treated
Renal and urinary disorders	Chromaturia	The clinical impact of these risks on patients is considered minimal in relation to the severity of the indication treated

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks:

There is no important identified risk related to the use of idebenone.

Important Potential Risks:

Important Potential Risk 1: Abnormal liver function test and hepatitis

Risk-benefit impact: During clinical development, the frequency and severity of increased liver enzymes and blood bilirubin were similar in patients receiving idebenone and placebo. Many patients had events that were confounded by other factors. This potential risk will be further evaluated in the post-marketing period.

Important Potential Risk 2: Blood count abnormalities

Risk-benefit impact: During clinical development, the frequency and severity of blood count abnormalities were similar in patients receiving idebenone and placebo. Many patients had events that were confounded by other factors. This potential risk will be further evaluated in the post-marketing period.

Missing Information:

Missing information 1: Use in children under 14 years of age with LHON
Risk-benefit impact: The safety of idebenone in patients under 14 years of age has not been established. The risk of use in these age groups cannot be defined based on the available evidence.

Missing information 2: Use in patients with hepatic impairment
Risk-benefit impact: idebenone has not been evaluated in patients with hepatic impairment. The risk of use in patients with hepatic impairment cannot be defined based on the available evidence.

Missing information 3: Use in patients with renal impairment
Risk-benefit impact: idebenone has not been evaluated in patients with renal impairment. The risk of use in patients with renal impairment cannot be defined based on the available evidence.

Missing information 4: Use in pregnancy and lactation in patients with LHON
Risk-benefit impact: Idebenone has not been evaluated in pregnant and breastfeeding patients. Although, non-clinical data has not shown any evidence of embryofoetal toxicity or teratogenicity, the risk cannot be defined based on the available evidence. Studies in rats have shown that idebenone is excreted into maternal milk. Therefore, a decision must be made whether to discontinue breast-feeding or to discontinue therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Missing information 5: Use in elderly patients with LHON
Risk-benefit impact: The safety of idebenone has not been established in elderly patients with LHON.

Missing information 6: Safety on long-term use
Risk-benefit impact: The safety of long-term use of idebenone has not been established. The risk of long-term use cannot be defined based on the available evidence.

Missing information 7: Potential for inhibition of P-gp
Risk-benefit impact: The potential for inhibition of P-gp of idebenone has not been thoroughly investigated.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Safety on long-term use previously classified as missing information is removed from the list of safety concerns.

A total of 229 patients were originally enrolled in the study; 224 received treatment with Raxone® and were therefore included in the Safety population.

PAROS study provides a relatively long assessment of safety and efficacy, with 221 LHON patients treated with Raxone® for more than 12 months, 159 patients for more than 24 months and 103 patients for more than 36 months, with a mean duration of exposure of 765.4 days (SD 432.6 days).

A total of 130 patients (58.0% of the Safety population) reported 382 TEAEs. Eleven (4.9%) patients reported 17 severe AEs. Fifty (22.3%) patients reported 82 AEs that were considered by the Investigator to be drug-related. Thirty-four (15.2%) patients had AEs that led to discontinuation of Raxone® treatment. Twenty-five (11.2%) patients experienced serious TEAEs. There was one death in the study, in an 81-year-old male patient who died of terminal prostate carcinoma, which was assessed by the

Investigator as unrelated to Raxone. AEs reported by SOC and PT were reported by >5% of patients in the Safety Population.

Overview of treatment-emergent adverse events (Safety Population)

Category	Events	Patients	Days in treatment[1]	
			Mean (SD)	Min, max
Any TEAEs	382 (100.0%)	130 (58.0%)	388.7 (323.8)	0 - 1450
Drug-related[2] TEAEs	82 (21.5%)	50 (22.3%)	247.0 (237.9)	0 - 833
Severe TEAEs[3]	17 (4.5%)	11 (4.9%)	462.9 (441.8)	0 - 1251
Serious TEAEs[3]	31 (8.1%)	25 (11.2%)	461.8 (407.7)	0 - 1399
TEAEs leading to Raxone® treatment discontinuation	39 (10.2%)	34 (15.2%)	350.9 (272.2)	0 - 1111
TEAEs leading to temporary dose interruption	12 (3.1%)	9 (4.0%)	182.6 (163.9)	0 - 450
TEAEs leading to death	1 (0.3%)	1 (0.4%)	NA	NA

NA, not applicable; SD, standard deviation; TEAE, treatment-emergent adverse event
[1]Days since start of treatment at time of event
[2]As assessed by the Investigator or Sponsor
[3]Other than death
Source: PAROS CSR version 01, 20 Dec 2021

AEs within the SOC Metabolism and Nutrition Disorders were reported by 36 (16.1%) patients; 17 (7.6%) reported vitamin D deficiency and 13 (5.8%) reported folate deficiency. Among the 34 (15.2%) patients who reported events within the SOC General Disorders and Administration Site Conditions, 27 (12.1%) patients reported drug ineffective. Twenty-nine (12.9%) patients reported events within the SOC Investigations, where 15 (6.7%) patients reported ALT increased and GGT increased. Gastrointestinal Disorders were reported by 24 (10.7%) patients, with 15 (6.7%) reporting diarrhea.

System organ class Preferred term	Events	Patients	Days in treatment[1]	
			Mean (SD)	Min - max
Total AEs and patients with AEs	382 (100.0%)	130 (58.0%)	388.7 (323.8)	0 - 1450
Eye disorders	30 (7.9%)	22 (9.8%)	346.0 (260.0)	5 - 911
Gastrointestinal disorders	41 (10.7%)	24 (10.7%)	216.0 (229.0)	0 - 833
Diarrhea	17 (4.5%)	15 (6.7%)	163.9 (211.9)	0 - 827
General disorders and administration site conditions	37 (9.7%)	34 (15.2%)	384.5 (299.6)	0 - 1161
Drug ineffective	27 (7.1%)	27 (12.1%)	433.4 (267.9)	0 - 1111
Infections and infestations	29 (7.6%)	18 (8.0%)	375.8 (333.4)	0 - 1359
Injury, poisoning and procedural complications	19 (5.0%)	17 (7.6%)	559.9 (434.6)	30 - 1420

System organ class Preferred term	Events	Patients	Days in treatment[1]	
			Mean (SD)	Min - max
Investigations	58 (15.2%)	29 (12.9%)	390.6 (270.7)	0 - 1084
ALT increased	18 (4.7%)	15 (6.7%)	350.9 (289.7)	0 - 1084
GGT increased	18 (4.7%)	15 (6.7%)	439.6 (250.1)	1 - 811
Metabolism and nutrition disorders	46 (12.1%)	36 (16.1%)	512.9 (352.7)	3 - 1441
Vitamin D deficiency	18 (4.7%)	17 (7.6%)	489.5 (370.3)	3 - 1441
Folate deficiency	13 (3.4%)	13 (5.8%)	591.1 (389.6)	167 - 1317
Musculoskeletal and connective tissue disorders	18 (4.7%)	16 (7.1%)	339.7 (338.3)	6 - 1306
Nervous system disorders	24 (6.3%)	18 (8.0%)	441.0 (267.6)	17 - 898
Psychiatric disorders	20 (5.2%)	17 (7.6%)	404.1 (364.0)	0 - 1140

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; SD, standard deviation;
[1]Days since start of treatment at time of event
Source: PAROS CSR version 01, 20 Dec. 2021

Following assessment of the results obtained after Marketing Authorisation, long-term treatment with Raxone® was well-tolerated in patients with LHON with no new safety concerns.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Potential risk: Abnormal liver function test and hepatitis	
MedDRA terms	MedDRA SMQ: Hepatic disorders (SMQ code: 20000005)
Potential mechanisms	The exact mechanism of potentially associated with idebenone abnormal liver function test is unknown.
Evidence source and strength of evidence	Clinical trial data and post-marketing experience
Characterisation of the risk	In RHODOS there were 5 abnormal values observed in 4 idebenone-randomized patients (7.2%) at BL, compared to 6 abnormal values in 3 idebenone-randomized patients (5.5%) at End of Treatment (EOT). One patient (1.8%) (SNT-II-003-009) had an abnormal (>3x Upper Limit Normal (ULN) Aspartate Transaminase (AST) level at baseline, which was normal at EOT, and one patient (1.8%) (SNT-II-003-070) who had a normal AST level at BL, presented with an abnormal AST level (>5xULN) at EOT. This patient presented however with an abnormal Gamma-glutamyl Transferase (GGT) level (>5xULN) at both BL and EOT. Patient SNT-II-003-027 presented with

Potential risk: Abnormal liver function test and hepatitis	
	abnormal Alanine Transaminase (ALT), AST and GGT at both BL and EOT. Finally, patient SNT-II-003-096 presented with a very slight increase in total bilirubin between BL and EOT. A similar picture emerges for placebo-randomized patients in RHODOS with 1 normal and 4 abnormal GGT levels reported in 5 patients at BL, where a categorical worsening was observed by EOT in 2 patients. No abnormal liver enzyme levels were reported during the NICOSIA study. In IONIA, a two-category increase in AST to 5xULN was observed for 1 patient (4.5%) at the idebenone mid dose. In MICONOS, one patient (1.7%) receiving the low dose presented with a categorical decrease in GGT from 5xULN to 3xULN between BL and EOT. Also in MICONOS, one patient (1.7%) on the mid dose presented with a categorical increase to 3xULN and one patient (1.7%) with a categorical decrease from 3xULN between screening and BL. No changes in liver enzymes were reported for patients in the placebo group or the high dose group in MICONOS. One serious report of liver injury (SAN000098) originated from MICONOS Extension study. It regarded a 59 year-old female patient, who received idebenone (2250 mg/day, 5 tablets t.i.d). The subject had a relevant medical history of polyneuropathy, hypothyroidism, high blood pressure, cardiomyopathy, urinary incontinence, recurrent urinary tract infection, intermittent chest pain and depressive disorder and was under multiple comedications. There were three reports of fulminant hepatitis and cytolytic hepatitis from post marketing experience. The first report (SAN000126) is a fatal case that regarded a 40-year-old male patient who was included in a compassionate use program and received Mnesis for FRDA. This patient was on multiple concomitant medications (acetylsalicylate lysine, spironolactone, baclofen, bisoprolol fumarate, perindopril, alprazolam, paroxetine, macrogol). Furthermore, other causes such as viral hepatitis, septic shock and cardiogenic shock are plausible explanation for the fatal outcome. Overall, this case remains difficult to be coherently assessed since it lacks information on any etiological investigation, autopsy results and all circumstances surrounding death occurrence. The second report (SAN000230) concerned a 20-year-old male patient treated with Mnesis 7 mg/kg for FRDA. In July 2012, the patient was hospitalized due to a cytolytic hepatitis. As a result of the event, treatment with Mnesis was stopped and the subject’s health condition improved. However, the serious event of neurological decompensation, also reported in this case, occurred after Mnesis discontinuation. The information is sparse and incomplete and a coherent causal assessment cannot be made. This third report (SAN000279) concerns a 19-year-old male patient who started therapy with Mnesis on 1st August 2007 for FRDA. The patient's

Potential risk: Abnormal liver function test and hepatitis	
	medical history included FRDA, non-insulin dependent diabetes, sleep apnoea syndrome and left ventricular hypertrophy. The patient was hospitalized, presenting with encephalopathy likely of hepatic metabolic origin and experienced hepatitis fulminant. The patient experienced progressive degradation of his hemodynamic status associated with multi-system organ failure and cardio-respiratory arrest leading to death on 26th October 2014. This case was considered to be serious based on fatal seriousness criteria and assessed as related by the reporter. However, hepatitis has been reported with the use of concomitant medications Glucor (acarbose) and Xelevia (sitagliptin phosphate monohydrate) and individual cases of fulminant hepatitis with fatal outcome have also been reported with the use of Glucor. The intake of concomitant medications could therefore more plausibly explain the occurrence of the event due to the chronological criterion. Following medical review of this case, it was concluded that there are no elements to relate idebenone administration with the event of hepatitis fulminant. In LEROS, one patient from case SAN-000669 experienced a fatal alcoholic hepatic failure. The patient was taking Raxone 900 mg daily until 30-Nov-2018. The patient's medical history included alcohol abuse, alcoholic cirrhosis and pneumonia, alcohol dependence syndrome and liver fibrosis. On 11-Mar-2019, around 3,5 months after stopping Raxone, the patient was hospitalized due to weakness, headache and reduced amount of urine input. The patient had been consuming alcohol continuously for two weeks. His condition degraded and a final diagnosis of kidney injury stage III (acute renal failure), generalized inflammatory reaction, alcoholic cirrhosis and alcohol dependence syndrome (delirium tremens). Since admission, the patient was circulatory unstable with hypotension refractory to supply of catecholamines. Four days after admission the patient died. This event was not considered as related by both the Investigator and Sponsor to Raxone but rather to the patient's alcohol abuse. In addition Raxone was stopped several months before the fatal events. LEROS did not provide any additional data that would support further characterising the potential important risk of abnormal liver function tests and hepatitis or that would support confirmation of this risk as an identified important risk. The data obtained from this study were very similar to the known safety profile and the prevalence of such events in the DMD population in general. In PAROS study (PASS study SNT-IV-003), 48 events out of 382 were related to Abnormal liver function test and hepatitis: • GGT increased was experienced by 15 patients, corresponding to 18 events, out of which only four were considered as related to Raxone® by the Investigator and/or the Sponsor. All of the patients experiencing GGT increased events considered as related by the Investigator had a known medical history of alcohol consumption and despite Raxone® being considered as related, alcohol consumption was cited as the alternative

Potential risk: Abnormal liver function test and hepatitis	
	cause. In total, thirteen out of these 15 patients had a known history of alcohol consumption/abuse. • The 18 ALT increased events were experienced by 15 patients, out of which nine patients had known history of alcohol abuse. Six events were considered as related by the Investigator and/or the Sponsor. Two patients experiencing events considered as related to idebenone had a known history of alcohol abuse; one patient experienced increased ALT in the context of biliary lithiasis discovered less than 4 months after starting Raxone®. This case is described below. Of note, the remaining ALT events considered as related have been conservatively retained in the Clinical Trial database, even though they were considered not to be clinically significant by the Investigator in the safety database (case SAN-000701). • AST increased was experienced by 9 patients, out of which 5 had known history of alcohol abuse. Two events were considered as related to Raxone® by the Investigator and/or the Sponsor. One event was experienced by one patient with known medical history of alcohol consumption and the other related events refer to patient 20503007 experiencing the event in the context of biliary lithiasis.
Risk factors and risk groups	LHON patients, as a result of their debilitating disease, often suffer from reactive depression and may present behavioural traits of alcohol abuse and dependence which will predispose them to liver toxicity.
Preventability	Section 4.8 of the SmPC states that increased liver function tests and hepatitis have been reported when administering idebenone.
Impact on risk-benefit balance of the product	Mild elevations of liver function may have no impact on the patient. More severe hepatotoxicity may require cessation of medication and hospitalisation.
Public health impact	Mild elevations of liver function will have minimal impact on public health. More severe hepatotoxicity may result in additional health care resource and in patient care.

Potential risk: Blood count abnormalities	
MedDRA terms	MedDRA SMQ: Haematopoietic cytopenias (SMQ code: 20000027)
Potential mechanisms	The exact mechanism of idebenone-associated blood count abnormalities is unknown.
Evidence source and strength of evidence	Clinical trial data and post-marketing experience.

Potential risk: Blood count abnormalities	
Characterisation of the risk	Clinical studies Grouping together the six AE reports of blood test abnormalities observed in RHODOS, and using patient units in the denominator, the following incidence proportion can be calculated: idebenone: 10.8% ; Placebo: 0% AEs (regardless of causality) consistent with the medical condition "Blood dyscrasia" (i.e. an imbalance of components of the blood), were reported under the SOC Blood and Lymphatic System Disorders and the SOC Investigations from the following studies conducted in the FRDA indication: NICOSIA (double-blind, 6-months duration) • 27.3% of the patients on placebo • 16.7% of the patients on 180/360 mg/day idebenone • 0% of the patients on 450/900 mg/day idebenone and • 16.7% of the patients on 1350/2250 mg/day idebenone IONIA (double-blind, 6-months duration) • 0% of the patients on placebo • 0% of the patients on 450/900 mg/day idebenone and • 4.2% of the patients on 1350/2250 mg/day idebenone MICONOS (double-blind, 12-months duration): • 8.5% of the patients on placebo • 1.8% of the patients on 180/360 mg/day idebenone • 8.9% of the patients on 450/900 mg/day idebenone and • 15.3% of the patients on 1350/2250 mg/day idebenone IONIA Extension (open-label, non-comparative, 12-months duration) • 4.4% of the patients on 1350/2250 mg/day idebenone The review of blood test data from the above studies shows a slight decrease of WBC counts compared to Baseline in the MICONOS study and a slight decrease in the levels of mean corpuscular haemoglobin concentration (MCHC) in the IONIA Extension study. In both cases the changes were clinically silent and irrelevant (mean always within normal range). Disorders. Five (5) patients reported event under SOC Investigations, however these were 'blood cholesterol increased' and 'breath sounds abnormal'. Post-authorisation: Rare reports of hematologic disorders including agranulocytosis, anaemia, leukocytopenia and thrombocytopenia are listed in the SmPC of Mnesis (idebenone), the reference product marketed by Takeda in cognitive disorder. In PAROS study, ten events were related to the AESI Blood count abnormalities. Almost all of the events (9 events) belonged to the SOC Blood and lymphatic system disorders. The remaining event belonged to the SOC Neoplasms benign, malignant and unspecified (incl. cysts and polyps). Three events were considered related to Raxone® by the Investigator and/or the

Potential risk: Blood count abnormalities	
	Sponsor: Leukopenia (1) and one Neutropenia (1), and Macrocytosis (1). One serious event was reported (Chronic myeloid leukaemia). This event started more than two years after starting Raxone® (case SAN-000449) and was not considered as related by both the Investigator and Sponsor.
Risk groups or risk factors	No risk groups or risk factors could be identified.
Preventability	Section 4.8 of the SmPC states that blood count abnormalities during treatment with idebenone have been reported.
Impact on risk-benefit balance of the product	Mild blood count abnormalities would have little impact on the individual patient. Should more severe haematological toxicity occur, this would require cessation of medication and supportive therapy.
Public health impact	Typically, the events of blood dyscrasia reported with idebenone in the patient populations with LHON and FRDA were clinically silent and recovered spontaneously without discontinuation of the treatment. The potential impact of these findings on public health is therefore deemed to be minimal, especially in light of the recommendation to perform a complete blood cell count prior and during the treatment.

SVII.3.2. Presentation of the missing information

Missing information 1: Use in children under 14 years of age with LHON
Evidence source: Idebenone has not been evaluated in children with LHON under 14 years of age.
Population in need of further characterisation: The risk of use in children with LHON under 14 years of age cannot be defined based on available evidence and thus the safety profile in this population has been defined from routine pharmacovigilance activities and from PAROS study (PASS). The small number of patients under 14 years of age enrolled in PAROS study precludes any possible conclusion. Therefore the use of Raxone on these patients is still considered as missing information.

Missing information 2: Use in patients with hepatic impairment
Evidence source: Idebenone has not been evaluated in patients with hepatic impairment.
Population in need of further characterisation: The risk of use in patients with hepatic impairment cannot be defined based on available evidence and thus the safety profile in this population will be defined from routine pharmacovigilance activities, from PAROS study (PASS).

The small number of patients with hepatic impairment enrolled in PAROS study precludes any possible conclusion. Therefore the use of Raxone on these patients is still considered as missing information.

Missing information 3: Use in patients with renal impairment
Evidence source: Idebenone has not been evaluated in patients with renal impairment.
Population in need of further characterisation: The risk of use in patients with renal impairment cannot be defined based on available evidence and thus the safety profile in this population will be defined from routine pharmacovigilance activities, from PAROS study (PASS). The small number of patients with renal impairment enrolled in PAROS study precludes any possible conclusion. Therefore the use of Raxone on these patients is still considered as missing information.

Missing information 4: Use in pregnancy and lactation
Evidence source: Idebenone has not been evaluated in pregnant and breastfeeding patients.
Population in need of further characterisation: The risk of use in pregnant patients with LHON and their breastfed children cannot be defined based on available evidence and thus the safety profile in this population will be defined from routine pharmacovigilance activities.

Missing information 5: Use in elderly patients with LHON.
Evidence source: The safety of idebenone has not been evaluated in elderly patients with LHON.
Population in need of further characterisation: The risk of use of idebenone in elderly patients with LHON cannot be defined based on available evidence and thus the safety profile in this population will be defined from routine pharmacovigilance activities and from PAROS study (PASS). The small number of elderly patients enrolled in PAROS study precludes any possible conclusion. Therefore the use of Raxone on these patients is still considered as missing information.

Missing information 6: Potential for inhibition of P-gp
Evidence source: The potential for inhibition of P-gp of idebenone has not been thoroughly investigated.

Population in need of further characterisation:

The risk of the potential for inhibition of P-gp of idebenone in patients with LHON cannot be defined based on available evidence and this will be investigated in preclinical studies and potential drug-drug interactions will be defined from routine pharmacovigilance activities.

Part II: Module SVIII - Summary of the safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Abnormal liver function test and hepatitis Blood count abnormalities
Missing information	Use in pregnancy and lactation Use in children under 14 years of age with LHON Use in elderly patients Use in patients with hepatic impairment Use in patients with renal impairment Potential for inhibition of P-gp

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

The post-authorisation safety profile of idebenone will be evaluated through routine pharmacovigilance activities. These activities are fully described in the Pharmacovigilance System Master File.

III.2 Additional pharmacovigilance activities

Post Authorisation Safety Study with Raxone in LHON Patients (PAROS)

Study short name and title:

PAROS-A Non-interventional Study of Clinical Experience in Patients Prescribed Raxone® for the Treatment of Leber's Hereditary Optic Neuropathy (LHON)

Rationale and study objectives:

The aim of this PASS was to provide additional clinical information on the use of Raxone® in the treatment of LHON.

Primary Objective: To further evaluate the long-term safety profile of Raxone® in the treatment of patients with LHON when used under conditions of routine clinical care

Secondary Objectives:

To further evaluate the long-term effectiveness of Raxone in the treatment of patients with LHON when used under conditions of routine clinical care

To quantify discontinuation of treatment due to adverse events (AEs) or due to lack of or loss of therapeutic response

To further elucidate the risk of abnormal liver function tests and hepatitis

Study design:

This study was a multicentre, prospective, non-interventional post-authorisation safety study (PASS) of the clinical outcomes for patients with LHON treated with Raxone®.

No medication was provided as part of this study. Raxone® was obtained through commercial channels.

Study population:

Patient prescribed Raxone® for the treatment of LHON who have completed the informed consent

Milestones:

First Patient In (FPI)/ Start of Data Collection: Q2 2016

Last Patient Out (LPO)/End of Data Collection: Q2 2021

Interim Reports: Annual reports for inclusion in the Periodic Safety Update Report (PSUR), annual data snapshots

Final Report: 20-Dec-2021

III.3 Summary Table of additional Pharmacovigilance activities

Table III.1: On-going and planned additional PV activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

Part IV: Plans for post-authorisation efficacy studies

Table IV.1 Planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific requirements

There are no efficacy studies which are conditions to the marketing authorisation or specific requirements of idebenone.

Study (Status)	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorisation				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
None	Not applicable	Not applicable	Not applicable	Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1. Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important potential risk 1: Abnormal liver function test and hepatitis	**Routine risk communication:** SmPC section 4.8 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine Treatment should be initiated and supervised by a physician with experience in LHON
Important potential risk 2: Blood count abnormalities	**Routine risk communication:** SmPC section 4.8 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine Treatment should be initiated and supervised by a physician with experience in LHON
Missing information 1: Use in children under 14 years of age with LHON	**Routine risk communication:** SmPC sections 4.2, 5.1 and 5.2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine Treatment should be initiated and supervised by a physician with experience in LHON
Missing information 2: Use in patients with hepatic impairment	**Routine risk communication:** SmPC sections 4.2 and 4.4 PIL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine Treatment should be initiated and supervised by a physician with experience in LHON
Missing information 3: Use in patients with renal impairment	**Routine risk communication:** SmPC sections 4.2 and 4.4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Treatment should be initiated and supervised by a physician with experience in LHON
Missing information 4: Use in elderly patients	**Routine risk communication:** SmPC section 4.2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine Treatment should be initiated and supervised by a physician with experience in LHON
Missing information 5: Use in pregnancy and in breastfeeding patients with LHON	**Routine risk communication:** SmPC section 4.6 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine Treatment should be initiated and supervised by a physician with experience in LHON
Missing information 6: Potential for inhibition of P-gp.	**Routine risk communication:** SmPC section 4.5 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine Treatment should be initiated and supervised by a physician with experience in LHON

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of risk minimisation measures

Table Part V.3 1: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important potential risk 1: Abnormal liver function test and hepatitis	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None*
Important potential risk 2: Blood count abnormalities	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None *
Missing information 1: Use in children under 14 years of age with LHON	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None *
Missing information 2: Use in patients with hepatic impairment	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None *
Missing information 3: Use in patients with renal impairment	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None *
Missing information 4: Use in elderly patients with LHON	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

		Additional pharmacovigilance activities: None *
Missing information 5: Use in pregnancy and in breastfeeding patients with LHON	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None *
Missing information 6: Potential for inhibition of P-gp.	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None *

*The PASS study (PAROS) was completed on 09-Jul-2021 (Database locked) and the CSR was release on 20 Dec 2021. Currently no additional PV activities are active.

Part VI: Summary of the risk management plan

Summary of risk management plan for Raxone

This is a summary of the risk management plan (RMP) for Raxone®. The RMP details important risks of Raxone®, how these risks can be minimised, and how more information will be obtained about Raxone®'s risks and uncertainties (missing information).

Raxone®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Raxone® should be used.

This summary of the RMP for Raxone® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Raxone®'s RMP.

I. The medicine and what it is used for

Raxone® is authorised for the treatment of LHON (see SmPC for the full indication). It contains idebenone as the active substance and it is given by oral route.

Further information about the evaluation of Raxone®'s benefits can be found in Raxone®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage *https://www.ema.europa.eu/en/medicines/human/EPAR/raxone*.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Raxone®, together with measures to minimise such risks and the proposed studies for learning more about Raxone®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

If important information that may affect the safe use of Raxone® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Raxone® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Raxone®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	Abnormal liver function test and hepatitis Blood count abnormalities
Missing information	Use in children under 14 years of age with LHON Use in patients with hepatic impairment Use in patients with renal impairment Use in elderly patients Use in pregnancy and in breastfeeding patients Potential for inhibition of P-gp.

II.B Summary of important risks

Potential risk: Abnormal liver function test and hepatitis	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing experience
Risk factors and risk groups	LHON patients, as a result of their debilitating disease, often suffer from reactive depression and may present behavioural traits of alcohol abuse and dependence which will predispose them to liver toxicity.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None*

*The PASS study (PAROS) was completed on 09-Jul-2021 (Database locked) and the CSR was released on 20 Dec 2021. Currently no additional PV activities are active.

Potential risk: Blood count abnormalities	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing experience.
Risk groups or risk factors	No risk groups or risk factors could be identified.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None*

*The PASS study (PAROS) was completed on 09-Jul-2021 (Database locked) and the CSR was released on 20 Dec 2021. Currently no additional PV activities are active.

Missing information 1: Use in children under 14 years of age with LHON	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None*

*The PASS study (PAROS) was completed on 09-Jul-2021 (Database locked) and the CSR was released on 20 Dec 2021. Currently no additional PV activities are active.

Missing information 2: Use in patients with hepatic impairment	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None*

*The PASS study (PAROS) was completed on 09-Jul-2021 (Database locked) and the CSR was released on 20 Dec 2021. Currently no additional PV activities are active.

Missing information 3: Use in patients with renal impairment	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC

	Additional risk minimisation measures: None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None*

*The PASS study (PAROS) was completed on 09-Jul-2021 (Database locked) and the CSR was released on 20 Dec 2021. Currently no additional PV activities are active.

Missing information 4: Use in elderly patients with LHON	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None*

*The PASS study (PAROS) was completed on 09-Jul-2021 (Database locked) and the CSR was released on 20 Dec 2021. Currently no additional PV activities are active.

Missing information 5: Use in pregnancy and in breastfeeding patients with LHON	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None*

*The PASS study (PAROS) was completed on 09-Jul-2021 (Database locked) and the CSR was released on 20 Dec 2021. Currently no additional PV activities are active.

Missing information 6: Potential for inhibition of P-gp.	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None*

*The PASS study (PAROS) was completed on 09-Jul-2021 (Database locked) and the CSR was released

on 20 Dec 2021. Currently no additional PV activities are active.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Study short name:	**Purpose of the study:**
None	

Imposed mandatory additional pharmacovigilance activity (key to benefit risk)

II.C.2 Other studies in post-authorisation development plan

Imposed mandatory additional pharmacovigilance activity (key to benefit risk)

Description of activity (or study title if known)	**Milestone(s)**	**Due Date(s)**
None	Not applicable	Not applicable

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Available in electronic format

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table 1 Annex II: Planned and on-going studies

Study	**Summary of objectives**	**Safety concerns addressed**	**Protocol link Milestones**
None			

Table 2 Annex II: Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
Phase I open label study of the potential pharmacokinetic interaction of idebenone (150 mg film-coated tablet) with midazolam in healthy male volunteers Category 3	Primary • To evaluate the pharmacokinetics of midazolam in the presence of idebenone after repeated administration of idebenone as a film-coated tablet. Secondary • To obtain further safety and pharmacokinetic information after repeated administration of idebenone.	Potential for pre-systemic inhibition of CYP3A4	Final study report: 24 July 2017 Submitted 15 August 2017
Non-interventional PASS: In order to further investigate the safety of Raxone in the treatment of LHON patients, the MAH should generate data based on an agreed protocol from a drug exposure registry of patients prescribed Raxone for the treatment of LHON in clinical practice (SNT-IV-003). The registry should also be used to generate data on long-term effectiveness. Category 2	Primary • To further evaluate the long-term safety profile of Raxone in the treatment of patients with LHON when used under conditions of routine clinical care Secondary • To further evaluate the long-term effectiveness of Raxone in the treatment of patients with LHON when used under conditions of routine clinical care • To quantify discontinuation of treatment due to adverse events or due to lack of or loss of	Long term safety, Use in populations not studied in clinical trials: pregnancy and lactation, elderly, children under 14 years of age, hepatic impairment, renal impairment	CSR submission: 22-Dec-2021

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
	therapeutic response To further elucidate the risk of abnormal liver function tests and hepatitis		

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

PART A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority

Not applicable

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

There are no proposed or on-going studies meeting the requirements to be listed in Annex 3.

Study title	Protocol status	Version of protocol	Date of protocol version
None			

*

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable

Annex 7 - Other supporting data (including referenced material)

The Adverse Events (AEs) provided in the table below were received from Santhera products. The events occurring while patients were taking Catena® are displayed below, as well as AEs occurring while patient were taking Raxone® (split into solicited events and spontaneous events).

1) Adverse events reported to patients taking Catena®

SOC Preferred Term	Not serious	Serious	Total
Blood and lymphatic system disorders	**1**		**1**
Neutropenia	1		1
Cardiac disorders		**4**	**4**
Atrial fibrillation		1	1
Cardiac failure		1	1
Cardiac failure congestive		1	1
Cardio-respiratory arrest		1	1
Eye disorders	**3**		**3**
Dry eye	1		1
Eye pain	1		1
Visual acuity reduced	1		1
Gastrointestinal disorders	**31**	**2**	**33**
Abdominal discomfort	2		2
Abdominal pain	2		2
Abdominal pain upper	2		2
Anal fistula	2		2
Bowel movement irregularity	1		1
Constipation	1		1
Diarrhoea	9	1	10
Dyspepsia	1		1
Nausea	7		7
Vomiting	4	1	5
General disorders and administration site conditions	**30**	**6**	**36**
Asthenia	1		1
Chills	1		1
Condition aggravated	2	1	3
Crying	1		1
Death		1	1
Drowning		1	1
Drug ineffective	19		19
Drug intolerance	1		1
Fatigue	2	1	3
Illness	1		1
Inflammation		1	1
Malaise	2		2

Swelling face		1	1
Hepatobiliary disorders	**2**		**2**
Jaundice	1		1
Ocular icterus	1		1
Infections and infestations	**3**	**7**	**10**
Diarrhoea infectious	1		1
Pilonidal cyst	2		2
Pneumonia		2	2
Pneumonia bacterial		1	1
Pyelonephritis		1	1
Respiratory tract infection		1	1
Sinusitis		1	1
Upper respiratory tract infection		1	1
Injury, poisoning and procedural complications	**3**	**1**	**4**
Exposure during pregnancy	1		1
Fall	1		1
Intentional product use issue	1		1
Upper limb fracture		1	1
Investigations	**8**	**1**	**9**
Aspartate aminotransferase increased	2		2
Blood bilirubin increased	1		1
Hepatic enzyme increased	3	1	4
Weight increased	1		1
White blood cell count decreased	1		1
Metabolism and nutrition disorders	**3**	**2**	**5**
Decreased appetite	2		2
Dehydration		1	1
Hyperkalaemia		1	1
Lactose intolerance	1		1
Musculoskeletal and connective tissue disorders		**3**	**3**
Muscular weakness		1	1
Osteonecrosis		1	1
Scoliosis		1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		**1**	**1**
Adenoid cystic carcinoma		1	1
Nervous system disorders	**10**	**5**	**15**
Amnesia	1		1
Balance disorder	1	1	2
Cerebrovascular accident		2	2
Coordination abnormal		1	1
Dizziness	3		3
Headache	4		4
Seizure		1	1
Somnolence	1		1
Pregnancy, puerperium and perinatal conditions	**2**	**1**	**3**

Normal newborn	1		1
Pre-eclampsia		1	1
Pregnancy	1		1
Psychiatric disorders	**6**	**2**	**8**
Agitation	1		1
Bipolar disorder		1	1
Depression	2		2
Inappropriate affect	1		1
Insomnia	1		1
Mania		1	1
Mood altered	1		1
Renal and urinary disorders	**2**	**1**	**3**
Chromaturia	2	1	3
Respiratory, thoracic and mediastinal disorders		**1**	**1**
Dyspnoea		1	1
Skin and subcutaneous tissue disorders	**4**	**2**	**6**
Acne conglobata	1		1
Pruritus	2	1	3
Rash	1	1	2
Social circumstances	**1**		**1**
Breast feeding	1		1
Surgical and medical procedures	**1**		**1**
Cataract operation	1		1
Vascular disorders		**1**	**1**
Circulatory collapse		1	1
Grand Total	**110**	**40**	**150**

2) Adverse events reported to patients taking Raxone® for all indications (spontaneous sources and non-interventional studies)

SOC Preferred Terms	**Not serious**	**Serious**	**Total**
Blood and lymphatic system disorders		**1**	**1**
Lymphadenopathy		1	1
Cardiac disorders	**1**	**1**	**2**
Palpitations	1		1
Wolff-Parkinson-White syndrome		1	1
Ear and labyrinth disorders	**1**		**1**
Tinnitus	1		1
Eye disorders	**4**	**1**	**5**
Eye pain	1		1
Visual acuity reduced	1		1
Visual impairment	2	1	3
Gastrointestinal disorders	**33**	**4**	**37**
Abdominal pain	3		3
Abdominal pain lower	1		1

Abdominal pain upper	5		5
Barrett's oesophagus		1	1
Bowel movement irregularity	1		1
Chronic gastritis	1		1
Diarrhoea	7		7
Dyspepsia	3		3
Dysphagia	1		1
Epulis	1		1
Functional gastrointestinal disorder		1	1
Gastrointestinal disorder	1		1
Haematochezia		1	1
Nausea	6		6
Vomiting	3	1	4
General disorders and administration site conditions	**52**	**8**	**60**
Asthenia	1	1	2
Condition aggravated	1		1
Death		5	5
Disease progression	2		2
Disease recurrence	1		1
Drug ineffective	13		13
Fatigue	3	1	4
Gait disturbance	1		1
General physical health deterioration	1		1
Inflammation	1		1
Malaise	1	1	2
No adverse event	18		18
Pre-existing condition improved	1		1
Pyrexia	2		2
Therapeutic product effect incomplete	1		1
Therapeutic response unexpected	5		5
Hepatobiliary disorders	**1**	**1**	**2**
Hepatic cytolysis	1		1
Hepatic steatosis		1	1
Immune system disorders	**1**		**1**
Hypersensitivity	1		1
Infections and infestations	**3**		**3**
Bronchitis	1		1
Nasopharyngitis	1		1
Rhinitis	1		1
Injury, poisoning and procedural complications	**77**	**1**	**78**
Accidental underdose	1		1
Exposure during pregnancy	1		1
Intentional overdose	1		1
Intentional product misuse	2		2
Intentional product use issue	2		2

Off label use	30		30
Prescription drug used without a prescription	2		2
Product administered to patient of inappropriate age	16		16
Product dose omission issue	1		1
Product use in unapproved indication	4		4
Product use issue	9		9
Radius fracture		1	1
Underdose	8		8
Investigations	**16**	**1**	**17**
Alanine aminotransferase increased	4		4
Aspartate aminotransferase increased	3		3
Blood bilirubin increased	1		1
Blood cholesterol increased	1		1
Blood creatinine increased	1		1
Blood thyroid stimulating hormone increased	1		1
Blood uric acid increased	1		1
Gamma-glutamyltransferase increased	3		3
Hepatic enzyme increased	1		1
Prostatic specific antigen increased		1	1
Metabolism and nutrition disorders	**2**		**2**
Decreased appetite	2		2
Musculoskeletal and connective tissue disorders	**6**	**2**	**8**
Arthralgia	2	1	3
Back pain	3	1	4
Muscle twitching	1		1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**2**	**3**
Malignant neoplasm of unknown primary site		1	1
Metastases to lung		1	1
Uterine leiomyoma	1		1
Nervous system disorders	**9**	**6**	**15**
Dementia		1	1
Dizziness	1		1
Dyskinesia		1	1
Haemorrhage intracranial		1	1
Headache	7	1	8
Loss of consciousness		1	1
Neuropathy peripheral		1	1
Syncope	1		1
Pregnancy, puerperium and perinatal conditions		**2**	**2**
Abortion		1	1
Pregnancy on oral contraceptive		1	1
Product issues	**1**		**1**
Product complaint	1		1
Psychiatric disorders	**8**	**16**	**24**
Aggression		1	1

Completed suicide		1	1
Depression		2	2
Hallucination		2	2
Hallucination, auditory		2	2
Hallucination, visual	1		1
Hallucinations, mixed		1	1
Insomnia	2	1	3
Panic attack	1		1
Psychotic disorder		1	1
Restlessness	2	1	3
Sleep disorder	1		1
Social avoidant behaviour		1	1
Stress	1		1
Suicidal behaviour		1	1
Suicidal ideation		2	2
Renal and urinary disorders	**4**		**4**
Chromaturia	2		2
Polyuria	1		1
Renal pain	1		1
Respiratory, thoracic and mediastinal disorders	**6**	**2**	**8**
Cough	1		1
Dyspnoea	1	1	2
Epistaxis	1	1	2
Increased bronchial secretion	1		1
Lung disorder	1		1
Rhinorrhoea	1		1
Skin and subcutaneous tissue disorders	**5**	**1**	**6**
Hyperhidrosis	1		1
Pruritus	2	1	3
Rash	1		1
Urticaria	1		1
Surgical and medical procedures		**1**	**1**
Hospitalisation		1	1
Vascular disorders		**1**	**1**
Hypertension		1	1
Grand Total	**231**	**51**	**282**

3) Adverse events reported to patients taking Raxone® for all indications (solicited sources)

SOC Preferred Term	**Not serious**	**Serious**	**Grand Total**
Blood and lymphatic system disorders	**13**	**1**	**14**
Anaemia	3	1	4
Anaemia macrocytic	2		2
Leukopenia	2		2
Macrocytosis	2		2
Neutropenia	2		2

Neutrophilia	1		1
Thrombocytopenia	1		1
Cardiac disorders	**2**	**16**	**18**
Angina unstable		1	1
Arrhythmia	1		1
Cardiac arrest		3	3
Cardiac disorder		1	1
Cardiac failure congestive		1	1
Cardiomyopathy		1	1
Coronary artery disease		1	1
Myocardial infarction		2	2
Myocarditis		1	1
Palpitations	1	2	3
Pericardial effusion		1	1
Ventricular tachycardia		2	2
Ear and labyrinth disorders		**2**	**2**
Deafness unilateral		1	1
Inner ear disorder		1	1
Eye disorders	**5**		**5**
Ocular sarcoidosis	1		1
Photopsia	2		2
Uveitis	1		1
Vitreous floaters	1		1
Gastrointestinal disorders	**48**	**7**	**55**
Abdominal discomfort	2		2
Abdominal distension	2		2
Abdominal pain	5	1	6
Abdominal pain upper	4		4
Constipation	2	1	3
Diarrhoea	19		19
Dry mouth	1		1
Gastritis	1		1
Gastrointestinal haemorrhage		1	1
Intussusception		1	1
Nausea	8	1	9
Pancreatitis		1	1
Rectal haemorrhage	1		1
Salivary hypersecretion		1	1
Vomiting	3		3
General disorders and administration site conditions	**45**	**7**	**52**
Chest pain	1	2	3
Chills	2		2
Condition aggravated	7	1	8
Disease progression	5		5
Disease recurrence		1	1

Drug ineffective	20	2	22
Drug interaction	1		1
Fatigue	1		1
Granuloma	1		1
Multiple organ dysfunction syndrome		1	1
No adverse event	4		4
Oedema peripheral	1		1
Pyrexia	1		1
Therapeutic product effect decreased	1		1
Hepatobiliary disorders		**2**	**2**
Cholelithiasis		1	1
Hepatic failure		1	1
Immune system disorders		**2**	**2**
Anaphylactic shock		1	1
Hypogammaglobulinaemia		1	1
Infections and infestations	**27**	**22**	**49**
Adenovirus infection		1	1
Appendicitis		1	1
Bronchitis	2		2
Diverticulitis		1	1
Diverticulitis intestinal perforated		1	1
Fungal skin infection	1		1
Groin abscess		1	1
Hepatitis C	1		1
Infection	1		1
Influenza	1		1
Lower respiratory tract infection	4	1	5
Nasopharyngitis	7		7
Oral candidiasis	1		1
Pharyngitis	1		1
Pneumonia	1	8	9
Pyelonephritis		1	1
Respiratory tract infection	4	1	5
Subcutaneous abscess		1	1
Tonsillitis	1		1
Trichomoniasis		1	1
Upper respiratory tract infection	1		1
Urinary tract infection	1	1	2
Viral infection		2	2
Vulvovaginitis		1	1
Injury, poisoning and procedural complications	**17**	**8**	**25**
Accidental overdose	1		1
Accidental underdose	1		1
Ankle fracture		2	2
Contusion		1	1

Drug monitoring procedure not performed	1		1
Foreign body in gastrointestinal tract		1	1
Inappropriate schedule of product administration	5		5
Intentional underdose	1		1
Joint dislocation		1	1
Ligament rupture		1	1
Off label use	1		1
Overdose	1		1
Paternal exposure before pregnancy	2		2
Paternal exposure during pregnancy	2		2
Paternal exposure timing unspecified	1		1
Respiratory fume inhalation disorder		1	1
Thermal burn		1	1
Wrong technique in product usage process	1		1
Investigations	**161**	**11**	**172**
Alanine aminotransferase increased	39		39
Aspartate aminotransferase increased	28		28
Bilirubin conjugated increased	1		1
Blood alkaline phosphatase increased	3		3
Blood bilirubin increased	8		8
Blood bilirubin unconjugated increased	1		1
Blood creatine phosphokinase increased	5	2	7
Blood lactate dehydrogenase increased	7		7
Blood potassium decreased		1	1
Blood triglycerides increased	1		1
Brain natriuretic peptide increased		1	1
Catheterisation cardiac		1	1
Eosinophil count decreased	1		1
Gamma-glutamyltransferase increased	29	2	31
Haematocrit decreased	2		2
Haemoglobin decreased	2		2
Liver function test abnormal	1	1	2
Liver function test increased	2		2
Lymphocyte count decreased	1		1
Lymphocyte count increased	3		3
Mean cell haemoglobin increased	1		1
Mean cell volume increased	2		2
Monocyte count decreased	1		1
Monocyte count increased	2		2
Neutrophil count decreased	3		3
Neutrophil count increased	2		2
Occult blood	1		1
Oxygen saturation decreased		1	1
Platelet count decreased	3		3
Porphyrins urine	1		1

Red blood cell count decreased	3		3
Serum ferritin decreased	1		1
Transaminases increased	1		1
Urobilinogen urine increased		1	1
Weight decreased		1	1
White blood cell count decreased	4		4
White blood cell count increased	2		2
Metabolism and nutrition disorders	**1**	**3**	**4**
Decreased appetite	1	1	2
Diabetic ketoacidosis		1	1
Metabolic acidosis		1	1
Musculoskeletal and connective tissue disorders	**7**		**7**
Bone pain	1		1
Muscle spasms	2		2
Musculoskeletal stiffness	1		1
Myalgia	3		3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		**3**	**3**
Chronic myeloid leukaemia		1	1
Prostate cancer stage IV		1	1
Tonsil cancer		1	1
Nervous system disorders	**11**	**7**	**18**
Dizziness	1	1	2
Epilepsy	1	2	3
Headache	8		8
Migraine		1	1
Movement disorder		1	1
Multiple sclerosis		1	1
Syncope		1	1
Vocal cord paralysis	1		1
Pregnancy, puerperium and perinatal conditions	**3**		**3**
Normal newborn	2		2
Premature baby	1		1
Psychiatric disorders	**9**	**22**	**31**
Adjustment disorder with depressed mood		1	1
Alcohol abuse		3	3
Anxiety	1	1	2
Anxiety disorder		1	1
Completed suicide		1	1
Delirium tremens		1	1
Depression		2	2
Hallucination	1		1
Hallucination, visual	1	1	2
Insomnia	1		1
Major depression		1	1
Mental disorder	1		1

Middle insomnia	1		1
Panic attack	1	2	3
Psychotic behaviour		1	1
Psychotic disorder		1	1
Sleep disorder	1		1
Suicidal behaviour		1	1
Suicidal ideation		1	1
Suicide attempt		4	4
Tension	1		1
Renal and urinary disorders	**10**	**1**	**11**
Acute kidney injury		1	1
Chromaturia	7		7
Nephrolithiasis	1		1
Polyuria	2		2
Reproductive system and breast disorders		**1**	**1**
Uterine haemorrhage		1	1
Respiratory, thoracic and mediastinal disorders	**12**	**11**	**23**
Acute respiratory failure		1	1
Aspiration	1		1
Cough	4		4
Dyspnoea		1	1
Epistaxis	1		1
Haemoptysis	1		1
Nasal discomfort	1		1
Oropharyngeal pain	1		1
Pleural effusion		1	1
Pneumonia aspiration		2	2
Productive cough	2		2
Pulmonary embolism		1	1
Respiratory disorder		1	1
Respiratory distress		1	1
Respiratory failure		3	3
Sputum discoloured	1		1
Skin and subcutaneous tissue disorders	**3**	**4**	**7**
Decubitus ulcer	1		1
Drug reaction with eosinophilia and systemic symptoms		1	1
Eczema		1	1
Erythema	1		1
Hyperhidrosis	1		1
Rash maculo-papular		1	1
Toxic skin eruption		1	1
Social circumstances	**3**	**1**	**4**
Miscarriage of partner		1	1
Pregnancy of partner	3		3
Surgical and medical procedures		**1**	**1**

Cataract operation		1	1
Vascular disorders	**3**	**1**	**4**
Flushing	1		1
Hot flush	2		2
Venous thrombosis limb		1	1
Grand Total	**380**	**133**	**513**

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Annex 8 – Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
1.3	8 Sep 2015 EMEA/H/C/003834	Initial RMP approved at time of marketing authorisation
1.4	18 Apr 2017 EMEA/H/C/003834/IB/007	Pharmacovigilance Plan: Due date postponed for provision of the final study report for the category 3 study *"An open-label study to assess the potential for pre-systemic inhibition of cytochrome P450 3A4 (CYP3A) by idebenone in healthy male subjects using midazolam as a substrate"*
1.6*	8 Mar 2018 EMEA/H/C/003834/II/0008	Missing Information: Potential for pre-systemic inhibition of CYP3A4 removed based on results of DDI study (SNT-I-017)
1.7	28 May 2019 EMEA/H/C/003834/IB/0015	Use of new RMP template (Rev 2.0.1) New date for the provision of final study reports of two Category 2 studies (PART IV Plans for post-authorisation efficacy study)
1.8	17 October 2019 EMEA/H/C/003834/II/0016	Completed study resulting in the removal of a Specific Obligation under Part IV of the RMP
1.10**	14 November 2019 EMEA/H/C/003834/II/0018	Completed study resulting in the removal of a Specific Obligation under Part IV of the RMP
1.11	NA	NA
1.12	21 July 2021 EMEA/H/C/003834/IB/0028	Type IB variation to change due date of LEROS report
1.13	Superseded by version 1.15 as part of EMEA/H/C/003834/S/0029	Completed study resulting in the removal of a Specific Obligation under Part IV of this RMP
1.14	Superseded by version 1.16 as part of EMEA/H/C/003834/II/0031	Completed study resulting in the removal of a Specific Obligation under Part IIIof this RMP
1.15	Currently being reviewed EMEA/H/C/003834/S/0029	Updated as per the Request for Supplementary information on the procedure
1.16	Superseded by version 1.17 EMEA/H/C/003834/II/0031	Updated as per the Request for Supplementary information on the procedure
1.17	Currently being reviewed EMEA/H/C/003834/II/0031	Updated as per the Request for Supplementary information on the procedure
1.18	Submitted as part of closing sequences for EMEA/H/C/003834/S/0029 and EMEA/H/C/003834/II/0031	Merge of version 1.17 and 1.15

* RMP v1.5 had been submitted, however the RMP had been updated to address the RSI and v1.6 was the final approved version

**RMP v1.9 had been submitted, however the RMP had been updated to address the RSI and v 1.10 was the final approved version