25 June 2015
EMA/480039/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Raxone

International non-proprietary name: idebenone

Procedure No. EMEA/H/C/003834/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANCOVA	Analysis of covariance
ASMF	Active Substance Master File
ATP	Adenosine triphosphate
AUC	Area under the time versus concentration curve
CF	Counting fingers
CGIC	Clinical Global Impression of Change
CI	Confidence Interval
c_{max}	Maximum plasma concentration
(s)CRR	(spontaneous) Clinically Relevant Recovery
CRW	Clinically Relevant Worsening
CL/F	Apparent oral clearance
CPPs	critical process parameters
CRS	Case Record Survey
CYP	Cytochrome P450
DSC	Differential Scanning Calorimetry
EAP	Expanded Access Programme
ECG	Electrocardiogram
EU	European Union
EVICR.net	European Vision Institute Clinical Research Network
FRDA	Friedreich's ataxia
GC	Gas Chromatography
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene Bottles
HM	Hand motion
HPLC	High Performance Liquid Chromatography
HRQoL	Health-related quality of life
ICH	International Conference on Harmonisation
ICP-AES	Inductive coupled plasma atomic emission spectroscopy
IONIA	Idebenone effects On Neurological ICARS Assessments
IUPAC	International Union of Pure and Applied Chemistry
IR	Infrared
(m)ITT	(modified) Intent-to-Treat
LC-MS/MS	Liquid chromatography coupled with mass spectrometry
LD_{50}	Dose expected to cause the death of 50 per cent of a defined animal population
LHON	Leber's Hereditary Optic Neuropathy
K_{ow}	n-octanol/water partition coefficient
LOCF	Last observation carried forward
logMAR	Logarithm of the minimum angle of resolution
LOQ	Limit Of Quantitation
LP	Light perception
LVH	Left ventricular hypertrophy
MedDRA	Medical Dictionary for Regulatory Activities
MICONOS	Mitochondrial protection with Idebenone in Cardiological and Neurological Outcome Study
MMRM	Mixed Model Repeated Measures
MS	Mass Spectrometry
mtDNA	mitochondrial DNA
NMR	Nuclear Magnetic Resonance
NOAEL	No observed adverse effect level
OR	Odds Ratio
P-gp	P-glycoprotein
PASS	Post-authorisation safety study
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
PP	Polypropylene

PPK	Population PK
PT	(MedDRA) Preferred Term
QC	Quality Control
RGC	Retinal ganglion cells
RH	Relative Humidity
RNFL	Retinal nerve fibre layer
SD	Standard Deviation
S.E.M.	Standard Error of the Mean
t.i.d.	Three times daily (ter in die)
$t_{1/2}$	Apparent terminal half-life
t_{max}	Time to reach maximum plasma concentration
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
UV	Ultraviolet
VA	Visual Acuity
VAS	Visual Analog Scale
XRPD	X-ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The Applicant Santhera Pharmaceuticals (Deutschland) GmbH submitted on 4 May 2014 an Application for Marketing Authorisation to the European Medicines Agency (EMA) for Raxone, through the centralised procedure under Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 July 2013.

The Application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The Applicant applied for the following indication:

Raxone is indicated in patients 14 years of age and older with Leber's Hereditary Optic Neuropathy (LHON)

Raxone was designated as an orphan medicinal product EU/3/07/434 on 15 February 2007. Raxone was designated as an orphan medicinal product in the following indication: treatment of Leber's hereditary optic neuropathy.

The legal basis for this Application refers to:

Hybrid Application (Article 10(3) of Directive No 2001/83/EC)

The Application submitted is composed of administrative information, complete quality data and appropriate non-clinical and clinical data.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the Applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Mnesis 45 mg tablets
- Marketing authorisation holder: Takeda Italia Farmaceutici S.p.A

- Date of authorisation: 01-05-1993
- Marketing authorisation granted by:

  Member State (EEA): Italy

  - National procedure
- Marketing authorisation number: A.I.C N 027586015

■ Medicinal product authorised in the Community/Members State where the Application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Mnesis 45 mg tablets
- Marketing authorisation holder: Takeda Italia Farmaceutici S.p.A
- Date of authorisation: 01-05-1993
- Marketing authorisation granted by:

  Member State (EEA): Italy

  - National procedure
- Marketing authorisation number: A.I.C N 027586015

Protocol assistance

The Applicant received Protocol Assistance from the CHMP on 19 November 2009. The Protocol Assistance pertained to clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the Application.

A Marketing Authorisation in the EEA was withdrawn by the applicant on 17 January 2013 before authorisation.

A Marketing Authorisation in Canada in a different indication was withdrawn on 30 April 2013 by the applicant after authorisation.

1.2. Manufacturers

Manufacturer responsible for batch release

Santhera Pharmaceuticals (Deutschland) GmbH
Marie-Curie Strasse 8
795390 Lörrach
Germany

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: John Joseph Borg

Co-Rapporteur: Andrea Laslop

- The Application was received by the EMA on 4 May 2014.
- The procedure started on 28 May 2014.
- The Rapporteur's initial Assessment Report was circulated to all CHMP members on 13 August 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 August 2014.
- PRAC RMP advice and assessment overview were adopted by PRAC on 11 September 2014.
- During the meeting on 25 September 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 December 2014.
- The Rapporteurs circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 January 2015.
- PRAC RMP advice and assessment overview were adopted by PRAC on 12 February 2015.
- During the CHMP meeting on 26 February 2015 the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 April 2015.
- The Rapporteurs circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 28 April 2015.
- PRAC RMP advice and assessment overview were adopted by PRAC on 7 May 2015.
- During the CHMP meeting on 19 May 2015, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 21 May 2015 the CHMP agreed on a second list of outstanding issues to be addressed in writing by the applicant. The applicant submitted the responses to the second CHMP consolidated List of Outstanding Issues on 28 May 2015.
- The Rapporteurs circulated the Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 4 June 2015.
- PRAC RMP advice and assessment overview were adopted by PRAC on 11 June 2015.
- During the meeting on 25 June 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation under exceptional circumstances to Raxone.
- Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Raxone as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designation.

2. Scientific discussion

2.1. Introduction

Problem statement

Leber's hereditary optic neuropathy (LHON) is a maternally inherited disease characterized by acute or sub-acute painless vision loss in one eye, generally followed by a similar vision loss in the second eye in a matter of weeks or few months (typically 2-4 months). Initially, in the acute phase, LHON patients experience a rapid and severe loss of visual acuity (VA) and colour vision associated with dense central or centrocecal scotoma. Fundus changes have been reported to occur in the pre-symptomatic phase, while in other cases, the fundus looks entirely normal. In the chronic phase of the disease, the optic discs become atrophic, starting usually within six weeks of disease onset. Most patients (~97 %) progress to a bilateral VA of 20/200 or worse within 1 year of disease onset. This fixed bilateral symmetric visual deficit remains for most patients life-long within the legal definition of blindness.

The prevalence of LHON is not very well established but estimated at 1/15,000 to 1/50,000 worldwide. LHON typically affects young adult male patients with a mean age of onset of 18-35 years, but women, small children and patients over 60 years of age can also be affected. Risk factors suggested in the scientific literature to promote the development of LHON include alcohol and tobacco consumption, although the association with the disease appears somewhat controversial.

Most LHON patients have visual loss as the only manifestation of the disease, but rare cases also present with cardiac (Wolff-Parkinson-White, Lown-Ganong-Levine, and long QT syndromes) and neurological manifestations (Leber plus; Bower et al. 1992).

LHON is caused by mutations in the mitochondrial DNA (mtDNA), whereby three point mtDNA mutations account for more than 90% of all LHON cases in the European Union (EU): m.11778G>A (ND4 subunit), m.14484T>C (ND6 subunit), and m.3460G>A (ND1 subunit). The m.11778G>A mutation generally is the most common point mutation in individuals, although there is considerable variation in the relative frequency worldwide. All of the three main primary LHON mutations result in amino acid changes in complex I (NADH:ubiquinone oxidoreductase) of the mitochondrial respiratory chain. In LHON patients, this change leads to a defect in complex I and disrupts the electron transport chain. However, the mutations are not always associated with a measurable respiratory chain abnormality. Experimental evidence connects complex I dysfunction to elevated levels of oxidative stress, reduced mitochondrial membrane potential and, as a consequence, reduced adenosine triphosphate (ATP) synthesis.

While in most cases, LHON leads to permanent vision loss, a minority of patients show spontaneous recovery of visual acuity by a mechanism that is not yet understood. Visual recovery, when it occurs, generally happens slowly between 6 and 12 months after the onset of the initial vision loss; however, sudden dramatic improvement in vision have also been reported to occur even many years after symptom onset. Publications in the scientific literature (Sadun et al. 2011 & Gueven et al., 2013) suggest that mitochondrial impairment initially, in the acute stage of the disease, results in retinal ganglion cells (RGCs) becoming inactive but remaining viable. This state can last for prolonged periods of time, so that functional recovery may be possible. With time, reduced efficiency of ATP synthesis and increased oxidative stress are believed to sensitize RGCs to apoptosis and the retinal nerve fibre layer (RNFL) gradually degenerates, leading to permanent vision loss.

Subjects with the m.14484T>C mutation have a 37–71% chance of some degree of visual improvement, while those with the m.11778G>A mutation only have a small chance around 4%. Subjects with the m.3460G>A mutation are reported to have a chance of recovery somewhere between those with the m.14484T>C and m.11778G>A mutations but the number of individuals bearing this mutation is too small to derive robust figures (Fraser et al., 2010). Positive prognostic features for visual recovery include a favourable mutation status and an age of disease onset less than 20 years. It has also been suggested that thicker RNFL and larger optic disc vertical diameter may be associated with a better visual prognosis (Fraser et al., 2010).

About the product

The active substance in Raxone is idebenone, which is a short-chain benzoquinone derivative and a synthetic analogue of ubiquinone (coenzyme Q10). Idebenone exerts antioxidant properties and by inhibiting lipid peroxidation may be able to protect cell membranes and mitochondria from oxidative damage. The proposed mechanism of action in LHON is that idebenone mitigates inactive-but-viable retinal ganglion cell dysfunction by shuttling electrons onto complex III of the mitochondrial transport chain, thereby bypassing the deficient complex I, restoring production of cellular energy and decreasing oxidative stress in affected cells.

The proposed indication for Raxone was treatment of patients 14 years of age and older with Leber's Hereditary Optic Neuropathy. Raxone is available as 150 mg film-coated tablets. The proposed dosing regimen is 900 mg/day administered as 2 tables three times a day.

Type of Application and aspects on development

This Application for a marketing authorisation of Raxone is an Application using Mnesis 45 mg tablets as reference medicinal product. Mnesis 45 mg tablets have been authorised in Italy since 1993 for treatment of cognitive and behavioural deficits due to cerebral pathologies of vascular or degenerative origin. Mnesis contains the same active substance as Raxone and is also administered via the oral route. The Applicant claimed that bioequivalence cannot be demonstrated through bioavailability studies and no studies against the reference product were provided. This was justified by the Applicant by the differences in the strength, daily dose and target population. The Application for Raxone only referred in certain areas to Mnesis, in particular to non-clinical data, and in all these areas there was no need for bioequivalence or comparable bioavailability studies to the reference product (see relevant sub-sections of sections 2.3. and 2.4. where reference to Mnesis is made). For these reasons, the CHMP agreed that no studies against the reference product were necessary.

The Application was supported by quality, non-clinical and clinical data including the results of one double-blind, randomised, placebo-controlled Phase II trial, RHODOS, investigating the efficacy, safety and tolerability of idebenone in the treatment of patients with LHON's disease. Additional efficacy and safety data in the target population were provided from an expanded access program (EAP) and a natural history case record survey (CRS). The latter data had not been available in a previous Application made in 2011 which was withdrawn in 2013. Supportive safety data were furthermore available from the clinical development program in Friedreich's ataxia (FRDA) as well as from post-marketing reports.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as immediate release film-coated tablets containing 150 mg of idebenone as active substance.

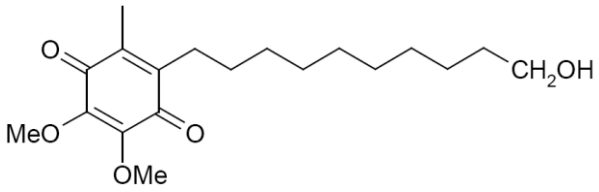
Other ingredients are: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone K25, magnesium stearate, colloidal silica, macrogol 3350, polyvinyl alcohol, talc, titanium dioxide and sunset yellow FCF (E110), as described in section 6.1 of the SmPC.

The product is available in high density polyethylene (HDPE) bottles with a polypropylene (PP) twist-off cap, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of the active substance idebenone is 2-(10-hydroxydecyl)-5,6-dimethoxy-3-methyl-2,5- cyclohexadiene-1,4-dione (IUPAC), corresponding to the molecular formula $C_{19}H_{30}O_5$ and has a relative molecular mass 338.44 g/mol. It has the following structure:



The structure of the active substance has been confirmed by IR, MS, NMR (^{13}C and ^{1}H), X-ray crystallography, and UV, all of which support the chemical structure.

It appears as a yellow-orange crystalline, non-hygroscopic powder. It is insoluble in water and freely soluble in ethanol. No dissociation constant has been calculated because idebenone has neither basic nor acidic function. Its $logP_{oct/wat}$ was found to be 3.93 at 25°C.

Idebenone is achiral. Two structurally distinct crystal forms are known and the most thermodynamically stable form has constantly been produced with the current process.

Manufacture, characterisation and process controls

Idebenone is manufactured by a simple two-step chemical synthesis from starting materials sourced from a different supplier. Idebenone is supplied by two different manufacturers both of which use the same manufacturing process. There is no isolated intermediate in the process. The reagents and solvents are common in chemical synthesis. Conventional chemical reactions are used. The final purification is performed by re-crystallisation in two different solvent mixtures. Reprocessing of the crystallisation step is foreseen and is acceptable. The synthesis has been described in sufficient detail and critical process parameters (CPPs) have been reported and are considered satisfactory. The in-process controls applied in the synthesis are adequate.

However since there is no isolated intermediate in the proposed two-step process, the CHMP considered that, as part of a more complete control strategy, the active substance starting materials should be considered at previous steps of the synthetic process. The applicant has committed and initiated work so that the starting materials will be redefined. The originally proposed starting material will be defined as an intermediate in the revised process. The route of synthesis of this intermediate remains the same and the additional steps will be carried out under GMP. The revised process will be implemented once the relevant GMP activities, such as validation of test methods, setting specifications, process validation are completed by November 2015. As an additional measure until the new process is fully implemented, the CHMP further required a new more stringent specification for the originally proposed starting material -isolated intermediated in the updated synthetic process- which is now put in place. In this regard batch data from eight recent batches of the originally proposed starting material have been presented and all met the revised specification. An updated comprehensive impurity discussion, including genotoxic impurities, has also been provided. The specifications and control methods for current starting material and reagents have been presented.

The CHMP considered that the information presented, the steps taken and the commitments provided by the applicant are sufficient to ensure that the quality of the product is warranted and give no rise concerns that could impact the safety of the medicinal product.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in double low-density polyethylene bags, sealed with plastic ties, and placed into a drum. The polyethylene bags comply with the relevant EC regulations and Ph. Eur. requirements.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Specification

The active substance specification includes appropriate tests and limits for: appearance and colour (visual inspection), appearance of solution (Ph. Eur.), identity (IR, melting range-), water content (Ph. Eur.), sulphated ash (Ph. Eur.), heavy metals (Ph. Eur.), residual catalysts (ICP-AES), assay (HPLC), related substances (HPLC), residual solvents (GC), particle size form (laser diffraction) and microbiological quality (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data on six full scale batches from one manufacturer and three full scale batches from the second manufacturer were provided. Analytical data of batches manufactured by both manufacturers indicate that a product of the same quality is produced at both manufacturing sites. The submitted batch analysis data also confirm that the manufacture is sufficiently robust and provide reassurance that the process yields active substance of consistent quality, complying with the specification.

Stability

Stability data on six commercial scale batches of active substance from the first manufacturer and three commercial scale batches from the second one stored in the intended commercial packaging for up to 60 months under long term conditions at 25 °C/60 % RH and for up to six months under accelerated

conditions at 40 °C/75 % RH according to the ICH guidelines were provided. The parameters tested were appearance, water content, related substances and assay. The same analytical procedures as for the release analysis were used, which had been shown to be stability indicating. The long term and accelerated data provided showed no sign of degradation or other change for any of the parameters studied.

The stability of the active substance was also investigated under stress conditions in solid state and solution. Stability under heat, light (as per the requirements of the ICH guideline Q1B), acidic, alkaline, neutral and oxidative conditions was studied. Results showed significant degradation under high pH only. However the two formed degradation products were observed in the long term or accelerated conditions stability studies and, therefore, were not included in the active substance specification.

Based on presented stability data, the proposed 5 years re-test period without any special storage conditions for idebenone are acceptable.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

Raxone is a film-coated tablet containing 150 mg of idebenone. Idebenone has been marketed as Mnesis sugar-coated tablets containing 45 mg of active substance for the treatment of cognitive disorders.

The development of Raxone film-coated tablets was focused on developing a similar formulation as Mnesis. The proposed dosage form has been developed taking into account that patients suffering from different mitochondrial diseases such as LHON, need a higher dose of idebenone.

The selected excipients are common tablet ingredients and their level has been justified. The individual excipients used in the coating as well as the colorant are of European Pharmacopoeia quality. The colorant also complies with Regulation (EU) 231/2012. The excipients have been varied on a quantitative basis to optimize the characteristics and performance of tablets. The particle size and compression force have been optimised throughout the development of the product.

Coating of the tablet was required to improve the appearance of the film-coated tablet. However, sugar coating was excluded for patients' acceptability and clinical reasons related to the underlying conditions of those patients. Therefore, a film-coated tablet containing 150 mg of idebenone has been developed as the appropriate dosage form for the disease and the target population. The selection of the coating has been adequately justified.

No incompatibilities with the excipients have been foreseen. This has been confirmed by stability data. Tablets of the same qualitative composition have been used throughout development.

The polymorphic stability of idebenone in film-coated tablets 150mg was investigated by Differential Scanning Calorimetry (DSC) and X-ray Powder Diffraction (XRPD). The investigation has demonstrated that the polymorph contained in the tablets remains unchanged, when tablets are stored for up to 5 years at 25°C/60% RH including up to for 4 months storage at 40°C/75% RH. Based on these studies, it was concluded that the manufacturing process of idebenone, as well as, storage and transport of the film-coated tablets 150 mg should exclude temperature excursions above 45°C in order to avoid polymorphic transformations.

The development of the dissolution method proposed for routine QC testing has been presented and the choice of the selected conditions and medium has been sufficiently justified. The method has been shown to be discriminatory with regard to relevant changes in manufacturing process parameters.

The manufacturing process has been optimised during scale up and process parameters ranges/ values have been set. The packaging material of Raxone film coated tablets is HDPE bottles with a polypropylene twist-off cap which complies with the relevant EU regulations.

Manufacture of the product and process controls

The manufacturing process consists of 9 steps as follows: mixing, granulation, drying, screening, blending I, blending II, compression, coating and packaging. It is a standard process and has been fully described. Critical steps have been identified and adequate in-process controls for this type of manufacturing process and pharmaceutical form have been put in place.

Major steps of the manufacturing process have been validated by a number of studies at both ends of the proposed batch size range. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release and shelf life specification include tests and limits for: appearance (visual), identification of idebenone (HPLC, UV), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.-UV) and microbial limits (Ph. Eur). The tests and acceptance criteria were set according to ICH guideline Q6A.

As no degradation products have occurred in batches during stability studies there are no specified degradation products in the specification. The impurities controlled in the active substance specification are process by-products and not degradation products. Considering also that, of the two identified polymorphs, one of them is obtained only under extreme conditions, which do not occur during the proposed manufacturing process, it is considered justified the specification not to include a test for polymorphic form.

Batch analysis data for three commercial scale batches were presented and all batches meet the specification.

Stability of the product

Stability data on three commercial scale batches stored under long term conditions for 60 months at 25 ºC / 60% RH and for up six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The stability batches of are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, dissolution, assay and degradation products and microbiological quality. The analytical procedures used were the same as for release and were shown to be stability indicating.

From the provided long-term and accelerated data there is no sign of degradation at any of the conditions studied. The level of unspecified impurities each remains below LOQ in most cases. All other tested parameters were within the specification limits and showed no trends.

A photostability study was performed according to ICH Q1B on one commercial scale batch. The provided results showed that the product is not light sensitive.

In-use stability testing to demonstrate that the product remains stable after the first opening of the multidose container was also performed. The testing period was 30 days, which represents the

anticipated period of use of the multidose container. The product did not show any significant change to any of the parameters tested (appearance, dissolution rate, assay, impurity profile, microbiological contamination). The in-use stability results confirm that Raxone 150 mg film-coated tablets are stable under these conditions.

Based on the presented data, the 5 year shelf life without any special storage conditions as stated in the SmPC are acceptable.

Adventitious agents

None of the excipients apart for lactose are of animal origin. It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, biological and pharmaceutical aspects

Information on development, manufacture and control of the active substance has been presented in a satisfactory manner. The current synthetic process is described in detail and the agreed control strategy is considered acceptable. However with a view to a more complete control strategy the applicant has committed to redefine the active substance starting material and thus update the manufacturing process to bringing additional synthetic steps under GMP by November 2015. The development, manufacture and controls of the finished product have been sufficiently documented and justified. The results of tests of active substance and finished product carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

To implement the revised and agreed synthetic process for the manufacture of the active substance from the agreed starting materials by November 2015.

2.3. Non-clinical aspects

2.3.1. Introduction

As the Application for Raxone is a hybrid Application, the non-clinical development programme partially relied on data of the reference product Mnesis. In addition, the Applicant presented primary pharmacology data in an animal model of LHON, safety pharmacology studies as well as some other non-clinical pharmacokinetic and toxicology studies performed with idebenone in order to support the use of Raxone in LHON. These non-clinical studies were reported to be compliant with Good Laboratory Practice.

2.3.2. Pharmacology

Primary pharmacodynamic studies

LHON disease is caused by genetic mutations in mtDNA that impair both mitochondrial function and the generation of cellular energy and expose energy-demanding tissues to oxidative stress. These cell-damaging events culminate in retinal ganglion cell (RGC) dysfunction and apoptotic cell death as well as atrophy of the optic nerve causing blindness of affected patients.

Idebenone is a synthetic analogue of ubiquinone (coenzyme Q10) and is proposed to function as an electron carrier in the mitochondrial electron transport chain, to inhibit lipid peroxidation and protect cell membranes and mitochondria from oxidative damage. The hypothesis presented in several published studies is that idebenone interacts with the electron transport chain and modulates mitochondrial electron flux. During this interaction, idebenone is reduced by complex I to 2H-idebenone which can return electrons to complex III, thereby providing a redox by-pass of complex I and stimulating alternative pathways to maintain cellular energy production.

Idebenone, in its reduced form, has been shown to inhibit reactive oxygen species formation and lipid peroxidation and to protect retinal cells from damage that arise through complex I inhibition. Published data from isolated mitochondria from different tissues suggest that idebenone, but not its metabolites QS10, QS6 or QS4, has an effect on cellular electron transfer which can help restoring mitochondrial respiration (Sugiyama et al., 1985; Degli Esposti et al., 1996; James et al., 2005; Haefeli et al., 2011).

In relation to the LHON indication, the Applicant has carried out one *in vitro* and several *in vivo* studies.

The results from the *in vitro* study using retinal cell line RGC-5 showed that idebenone increases RGC viability after treatment with rotenone, a potent mitochondrial complex I inhibitor. Statistically significant effects were observed after incubation with idebenone from concentrations ≥10nM. The observed effect was dependent on the duration of idebenone incubation prior to rotenone treatment with a greater extent of cell protection after pre-incubation for 2 days compared to 1 day.

The prevention of retinal neurotoxicity and the recovery of vision loss have furthermore been studied by the Applicant *in vivo* in a rodent LHON model. The LHON mouse model used for the *in vivo* studies are described in the literature (Ellouge et al. 2008, Abdeljalil et al. 2005). To simulate the situation of a mutated mitochondrial complex I, intravitreal injection of rotenone was used. Data from two studies indicate a slight protection by idebenone of retinal tissue, i.e. reduction of RGC loss, preservation of retinal thickness and protection from cell stress response, which was observed at doses of 400 mg/kg/day and 2000 mg/kg/day administered via the feed. This is in line with the scientific literature (Heitz et al, 2012). A second study showed that idebenone enhanced the recovery of vision in the same LHON mouse

model. When applying generally accepted conversions for the calculation of the human equivalent dose (species mouse conversion factor 12.3), the effect dose concentrations of idebenone used in the LHON mouse model were comparable to the clinical dose envisaged to be applied in man (900mg/day corresponding to 15mg/kg/day in a 60kg man). The estimates suggest that the concentration that could be reached in the human eye is comparable to the concentrations that showed efficacy *in vivo*.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been submitted and reference is made to the reference product for this hybrid Application, Mnesis. The CHMP considered that this approach was acceptable (see also section 2.1. type of Application and aspects on development) and that no further secondary pharmacodynamic data was needed.

Safety pharmacology programme

For safety pharmacology, the Application largely relies on the reference product Mnesis.

In addition, the Applicant performed both an *in vitro* and an *in vivo* study to investigate the potential cardiovascular and QT effects of idebenone. The hERG assay indicated inhibition of rapid delayed rectifier potassium current (IKr) only at nominal concentrations of idebenone far in excess of plasma levels achieved clinically. The *in vivo* study with telemetered Beagle dogs focussed on the effect of idebenone on the cardiovascular and respiratory system. Idebenone at 20, 100 and 500 mg/kg was without effect on blood pressure, heart rate, QT interval as well as other electrocardiogram (ECG) parameters, respiratory rate, and tidal and minute volume, both with respect to pre-dosing baseline values and to vehicle-treated controls. Idebenone was therefore considered to be without any influence on the cardiovascular and respiratory systems in the dog at single doses up to 500 mg/kg. Toxicokinetic data showed that the animals were adequately exposed to idebenone in the studies.

In conclusion, no effects on the QTc interval or other cardiologic effects were detected in these studies. These results were supported by the clinical findings that showed no effect on ECG morphology or the QTc interval in human volunteers or LHON patients receiving idebenone (see section 2.6.). Administration of idebenone was also without effect on the locomotor behaviour of the animals.

Pharmacodynamic drug interactions

With regards to the nonclinical testing for possible pharmacodynamic drug interactions of idebenone and its major metabolite Q10, reference is made to Mnesis. This was considered acceptable by the CHMP (see also section 2.1. type of Application and aspects on development).

2.3.3. Pharmacokinetics

In addition to a summary of the available data in the scientific literature, the Applicant provided results from two PK studies in mice to investigate absorption and distribution characteristics of idebenone. With regards to metabolism, excretion and PK drug interactions, reference is made to Mnesis and published literature.

PK studies have been performed in the same strain of mice used for the primary pharmacodynamic studies (see section 2.3.2.). The aim of these studies was to measure levels of idebenone and its unconjugated metabolites in the aqueous and vitreous humors of the eye as well as in plasma, following treatment with idebenone. Idebenone was either administered as a single oral (gavage) dose or in the diet (20-2000 mg/kg/day) over a period of three weeks. Idebenone after oral dosing in mice was quickly

absorbed. It was identified in the plasma and in the eye vitreous and aqueous humors within 15 min of administration. Idebenone was extensively metabolised and all of the metabolites measured in the plasma or eye fluids were present at higher levels than idebenone with the following order QS4>QS6>QS10>idebenone. The metabolite levels measured in the aqueous humor were approximately 5-fold higher than those reported in the vitreous humor. Terminal half-lives (t½) of the product after single oral (gavage) administration of idebenone and its major metabolites QS10, QS6 and QS4 were 1.70, 2.31, 6.22 and 5.84 hours, respectively. Overall the data indicate that idebenone enters the eye and is detectable in the aqueous and vitreous humor in concentrations which reflect its plasma profile.

In a detailed distribution study of idebenone's PK characteristics carried out by Torii et al. (1985) in rats and dogs, idebenone was found in relatively high concentrations within minutes after dosing in the liver and kidneys, plasma and later in the intestine and highly perfused organs. Reports showed that a considerable amount of unchanged idebenone was distributed in the mitochondrial fraction (34.4%). Due to a high first pass metabolism occurring in liver and intestinal mucosa < 1% of idebenone reaches systemic circulation. The metabolism of idebenone includes oxidation and shortening of the side chain resulting in the metabolites QS-10, QS-8, QS-6 and QS-4. These metabolites including the parent compound are further modified by conjugation (glucuronidation or sulfatation) resulting in conjugated forms of the metabolites as well as the parent compound. The main excretion route of idebenone and/or its metabolites is via urine in rats and dogs, which accounted for approximately 50-70 % of excretion. Studies performed in pregnant rats showed idebenone in both fetal plasma and tissues from pregnant rats, suggesting that the compound crossed the placenta. There were findings of idebenone at relatively low concentration in rat milk. No accumulation was reported after repeated dosing in rats and idebenone was excreted into milk in moderate amounts.

Idebenone, QS10, QS6 and QS4 were found to be largely protein-bound in rat, dog and human plasma. This information was used to support studies using human biomaterials performed to address the interaction potential of idebenone and QS10 on a range of Cytochrome P450 isoenzymes (see section 2.4.2.). This approach was deemed appropriate.

2.3.4. Toxicology

A summary of published studies has been provided to characterise the non-clinical toxicological profile of idebenone. In addition, one 39 weeks chronic toxicity study in dogs, one 4-week repeated toxicity study in rats and two genotoxicity studies performed by the Applicant were submitted. The Applicant furthermore referred to the reference product Mnesis, in particular to address the carcinogenic properties of idebenone.

Single dose toxicity

In single dose toxicity studies in mice and rats (Chiba et al., 1985), idebenone was found to be of low acute toxicity, presenting an LD_{50} value of more than >10000 mg/kg following oral and subcutaneous administration and 700-800 mg/kg after intraperitoneal administration. The direct cause of death seemed to be a respiratory failure by either route of administration.

Repeat dose toxicity

Idebenone was tested in oral repeat-dose toxicity studies in rats up to 26 weeks and Beagle dogs up to 39 weeks (Masuoka et al., 1985; Spicer and Wazeter, 1985; Suhara et al., 1985a, 1985b). In studies of ≥ 5 weeks rats and dogs were exposed to idebenone oral doses up to 500 mg/kg/day. In another short animal study, rats were dosed up to 2500 mg/kg/day for 2 weeks. Chromaturia due to coloured

metabolites, mainly the di-demethyl derivatives of QS4 and QS6 which were conjugated with glucuronic acid and sulphuric acid, was observed in both species. Coloured faeces were also seen in dogs occasionally.

In the 4-week rat toxicity study sponsored by the Applicant, Wistar rats were given oral (gavage) idebenone at dose levels of 20, 100 and 500 mg/kg body weight/day. The main effect of idebenone observed was local changes in the forestomach mucosa of the animals. Yellow colouration and mucosal thickening of the forestomach, occasionally accompanied by forestomach dilatation and the appearance of red spots in the fore- and glandular stomach was observed at necropsy. The histopathological findings comprised of dose-dependent increase in incidence/severity of submucosal inflammatory infiltrates, erosions and ulcerations of the forestomach, and hyperkeratosis, and epithelial and basal cell hyperplasia, focal necrosis and oedema.

In the 39-week chronic toxicity study in dogs (plus 8 week recovery), idebenone was administered at 500, 750 or 1000 mg/kg once daily by oral gavage. Vomiting of mucus, yellow or orange fluid and/or feed was recorded in all animals at all dose levels with the incidence showing a relationship to dose. Other signs, observed on occasion in isolated animals at 750 and 1000 mg/kg/day included salivation, abnormal consistency and discoloration of faeces, dark urine, shivering, whimpering and recumbency. There were no ophthalmological changes or changes in haematology, clinical biochemistry or urinalysis that were considered to be related to treatment with idebenone.

A decrease in mean heart rate was recorded in all idebenone treated groups in Weeks 26 and 39, especially in the male dogs, when compared to the controls. The decrease was occasionally apparent before dosing as well as after dosing. This effect was not dose dependent and was possibly secondary to an overall lower activity due to clinical signs combined with chronic low food consumption and loss of body weight, although there was no change in heart rate in the high dose animals at the end of the 8 week recovery period. Sinus arrhythmia and/or sinus pause, reflecting the decrease in heart rate, were seen in single animals after dosing at 750 or 1000 mg/kg/day (one animal at each dose level) in Weeks 13 and 26. There were no other effects on the amplitudes or intervals or changes in the wave-form of the electrocardiogram, including QTc, which were considered to be related to treatment with idebenone. Safety studies aiming at providing a greater understanding of the mechanistic effects of idebenone on vital functions, with special focus on the cardiovascular system, are reported in section 2.3.2.

A slight hypertrophy has been observed in the liver of two animals dosed at 1000 mg/kg/day but they were without any further indicator for liver injury.

The incidence and severity of the clinical signs, low food consumption and body weight losses were greatest in animals dosed at 1000 mg/kg/day and all changes reported were reversible.

Genotoxicity

Genotoxicity of idebenone was studied in an *in vitro* Ames test study and an *in vivo* mouse micronucleus test. Idebenone showed no genotoxic potential with respect to gene mutations in bacteria. Clastogenic potential was observed at high concentrations of idebenone, in the chromosome aberration test. This potential could be linked to the cytotoxic effect at high concentrations *in vitro*, which are most likely related to the redox properties of the substance. Furthermore, no genotoxic effects were observed in the *in vivo* mouse micronucleus test (tested at doses of 1250, 2500 and 5000 mg/kg once or 5000 mg/kg daily for four successive days).

Reference was also made to the reference product Mnesis, whereby SmPC Section 5.3 of Mnesis states that idebenone does not have any genotoxic potential.

Carcinogenicity

No carcinogenicity studies were performed by the Applicant. The Applicant referred to the reference medical product Mnesis. The SmPC of the reference product states that no carcinogenicity concerns are expected from the administration of idebenone. This approach was considered acceptable by the CHMP (see also section 2.1. type of Application and aspects on development).

Reproduction toxicity

Reference was made to Mnesis as well as published data in the scientific literature including a fertility and early embryonic development study, two embryofetal development studies in rats and rabbits and a pre and postnatal study in rats.

Fertility and early embryonic development in male and female rat studies at up to 500 mg/kg/day showed a higher rate of post-implantation losses and a lower number of live embryos. However, there were no other adverse effects at either dose on reproductive performance or on embryogenesis.

There was no effect on the development of the foetuses or growth of F1 animals observed in the teratology study, where a NOAEL of 500 mg/kg/day was identified. The main effect reported in this study was chromaturia. Similar results were obtained in a teratology study in rabbits where the only effect was again chromaturia at the highest dose administered (150mg/kg/day).

In pre- and postnatal studies in rats chromaturia was observed at 100-500 mg/kg/day and hypersalivation in the 500 mg/kg/day group. The effects reported where similar to those identified in the repeated dose toxicity studies.

Toxicokinetic data

Toxicokinetic data at steady state were generated in the 4-week toxicity study in rats and and in the 39-week dog toxicity study. At c_{max} at the respective NOAEL (500 mg/kg/day in rats and 750 mg/kg/day in dogs), concentrations of idebenone in plasma were 21 – 22 times higher in the rat and 25 – 28 times higher in the dog, when compared with the maximum mean concentration observed in man receiving 2250 mg Raxone, a dose 2.5 times higher than the envisaged dose of 900 mg/day Raxone in patients. The safety margin for the exposure, as measured by the AUC at steady-state for the NOAEL, ranged from 16 – 22 in the rat and 20 - 22 in dogs.

Local tolerance

Reference was made to Mnesis, which was considered acceptable by the CHMP (see also section 2.1. type of Application and aspects on development).

Other toxicity studies

Impurities

The sum of all impurities (identified and unidentified), with the exception of the mayor Impurity A, were below the qualification threshold of 1.0%. The specification limit for the Impurity A was set to 0.5%. Impurity A has been qualified with respect to genotoxicity and repeated dose toxicity in rats and dogs up to 0.68% (see non-clinical repeat toxicity results). Since Impurity A is a close analogue of idebenone, the suggested limit of <0.5% was considered acceptable and the impurity level could be considered qualified.

Photosafety

Idebenone does not absorb light within the range of natural sunlight at the wavelength of 290 - 700 nm. Therefore, in line with the ICH guideline S10 on Photosafety Evaluation of Pharmaceuticals (EMA/CHMP/ICH/752211/2012) there was no need for photosafety testing with idebenone.

2.3.5. Ecotoxicity/environmental risk assessment (ERA)

Based on epidemiological data on the prevalence of LHON in Europe taking into account published data from a meta-analysis for all three primary mtDNA mutations (Mascialino, 2011), the market penetration factor (Fpen) was calculated at 0.0000223. The Predicted Environmental Concentration (PECsurfacewater) for idebenone was consequently estimated at 0.01 µg/L. PECsurfacewater. The analysis was further refined based on data obtained during an information request to European registries, eye hospitals, and other database holders, resulting in a refined Fpen of 0.00000537 and a (PECsurfacewater of 0.0024 µg/L. The two values were right at or below the action limit of 0.01 µg/L as defined in the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2*, 2006). The n-octanol/water partition coefficient (Kow) of idebenone was determined at pH 8.2 to be 3.93 (log Kow). Since log Kow of idebenone was below the trigger of 4.5 screening for persistence, bioaccumulation and toxicity was not required.

Based on the available data, no adverse environmental effects were anticipated with the use of Raxone in LHON's disease and the CHMP considered that a Phase II (Tier A) environmental fate and effect analysis was not required.

Table 1 – Summary of main study results

Substance (INN/Invented Name):idebenone			
CAS-number (if available):			
PBT screening		***Result***	***Conclusion***
Bioaccumulation potential- log K_{ow}	OECD117	3.93	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$ refined (e.g. prevalence, literature)	0.0024	µg/L	< 0.01 threshold

2.3.6. Discussion on non-clinical aspects

From a non-clinical perspective, this Application was supported by primary pharmacology data in an animal model of LHON, safety pharmacology studies as well as some other non-clinical pharmacokinetic and toxicology studies. In addition, the Applicantion relied in certain aspects on the approved information of the reference product Mnesis and data published in the scientific literature.

The antioxidative effect of idebenone is widely studied and presented in the literature. The pharmacodynamic effect in the proposed indication is proposed to be mediated through a redox by-pass of complex I of the respiratory chain resulting in ATP generation despite the complex I dysfunction in LHON's disease. While data from *in vitro* and *in vivo* models at clinically relevant concentrations and dosages suggest that use of idebenone could be beneficial in LHON's disease, the mechanism of action of idebenone remains to be fully elucidated. The approach of the Applicant to only test idebenone in one in one animal species, was considered acceptable because the mitochondrial respiratory chain is conserved

across species. However, the LHON mouse model used in the primary pharmacodynamic studies did not fully replicate the disease in humans. Therefore, the CHMP considered that efficacy will need to be demonstrated in the clinical setting as the non-clinical data, though supportive, were not entirely conclusive.

With regards to safety pharmacology, based on the results of a hERG assay and a study with telemetered Beagle dogs, idebenone was considered to be without any influence on the cardiovascular and respiratory systems.

Non-clinical PK data showed that after oral administration, idebenone was rapidly absorbed. A high first pass metabolism occurring in liver and intestinal mucosa was reported in the scientific literature and excretion took place via the urine and bial.

As no specific human metabolite has been identified, mice, rats and dogs were considered to be the relevant animal models for the toxicity assessment. The Applicant's choice of species was therefore supported. In summary, the target organ in the rat was the forestomach, a finding reflecting low clinical relevance. In the dog study, clinical signs of gastrointestinal disturbances and emesis were the only signs of toxicity and considered likely due to non-specific, localized physiochemical irritation resulting from the very high doses of idebenone. Coloured urine and faeces were observed due to coloured metabolites.

Although adequate toxicokinetic data in dogs are lacking, some PK data indicate that a sufficient safety margin exists with regards to administration of a daily dose of 900 mg Raxone in humans. In addition, adequate exposure margins were obtained in rats and dogs. Non-clinical data generally revealed no safety concern for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity. In addition, according to the scientific literature and data for Mnesis, idebenone seems to have no carcinogenic potential, nor did it show any effect on the reproductive development, and there was no evidence of embryotoxic or teratogenic potential.

The lack of formal local tolerance studies as well as studies in juvenile animals was considered acceptable by the CHMP as the local toxicity findings observed were limited to the forestomach in rats (species specific tissue), no systemic toxicity and no target organ effects have been reported in dogs and no differential pharmacokinetics between adults and the proposed paediatric population (>14 years old) are expected. Furthermore, idebenone is not expected to induce dependence and hence, no studies to this end were required.

Finally, Phase I ERA was considered sufficient in light of the expected low environmental exposure when used in the intended orphan indication. No adverse environmental effects are to be expected with the use of idebenone.

2.3.7. Conclusion on the non-clinical aspects

Overall, the CHMP considered the non-clinical data presented to be adequate to support the Application for a marketing authorisation of Raxone in the treatment of LHON. Additional studies in suitable animal models and at relevant concentrations have been conducted and were considered supportive to establish the pharmacodynamic effects with regards to the proposed indication as well as the safety, PK and toxicological profile of idebenone. Cross-references to Mnesis as well as published data in the scientific literature were considered adequate by the CHMP and sufficient to justify absence of some of the non-clinical tests (see also section 2.1. type of Application and aspects on development).

2.4. Clinical aspects

2.4.1. Introduction

In support of this Application, results of a Phase II, double-blind, randomised, placebo-controlled study (SNT-II-003, RHODOS) in 85 LHON patients as well as from the single visit RHODOS Observational Follow-Up Study (SNT-II-003-OFU; RHODOS-OFU) were provided. Additional data were presented from an Expanded Access Programme (EAP; SNT-EAP-001) and a Natural History Case Record Survey (CRS; SNT-IR-006). Finally, data were submitted from 4 Phase I studies in healthy volunteers (SNT-I-001, SNT-I-002, SNT-I-003, and SNT-I-004) that investigated the pharmacokinetics of single and repeat dosing with Raxone. Reference was also made to literature reports of LHON patients treated with idebenone.

The Applicant also provided reports from clinical trials with idebenone in Friedreich's Ataxia (FRDA) patients, including one Phase II study (NICOSIA, 48 patients) and two Phase III efficacy, safety and tolerability studies (MICONOS, 232 patients and IONIA, 70 patients), which primarily served as supportive safety information (see section 2.6.).

Good Clinical Practice (GCP)

The clinical trials were performed in accordance with GCP as claimed by the Applicant.

The Applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies (excluding studies in populations other than LHON)

Type of Study	Study Identifier	Objectives of the Study	Study Design and Type of Control	Test Product, Dosage regimen, Route of Administration	Number of subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Bioavailability	SNT-I-001	Food effect on the PK of idebenone and its metabolites at two dose strengths	Open, parallel group, randomised, cross-over, single dose	Idebenone Group A: 150 mg Group B: 5 x 150 mg Oral administration	28	Healthy subjects	Single dose
Bioavailability	SNT-I-002	PK of idebenone and its metabolites after a single oral dose of 150 mg idebenone	Open, single 150 mg dose	Idebenone 150 mg Oral administration	8	Healthy subjects	Single dose
Bioavailability	SNT-I-003	PK of idebenone and its metabolites after multiple dosing at two dose strengths	Open, parallel group, randomised, single and repeated t.i.d dose	Idebenone Group A: 1x150 mg t.i.d. Group B: 5x150 mg t.i.d. Oral administration	25	Healthy subjects	2 weeks
Bioavailability	SNT-I-004	PK of idebenone and its metabolites after a single oral dose of 7 x 150 mg idebenone	Open, single 7 x 150 mg dose	Idebenone Single dose 7 x 150 mg Oral administration	8	Healthy subjects	Single dose
Clinical Efficacy and Safety	SNT-II-003 (RHODOS)	To determine whether administration of idebenone can improve visual function in Leber's Hereditary Optic Neuropathy patients	Randomized, double-blind, placebo-controlled, parallel group	Idebenone 2 x 150 mg t.i.d. Oral administration	85	Patients with LHON	6 months

Clinical Efficacy and Safety	SNT-II-003-OFU (RHODOS-OFU)	To assess visual acuity of LHON patients who participated in the SNT-II-003 trial and compare it to visual acuity at Visit 2/Baseline and Visit 5/Week 24 or last treatment visit of SNT-II-003	Single visit, observational follow-up study of patients participating in SNT-II-003	No treatment	Completed 60 patients (idebenone 41/placebo 19)	Patients with LHON	No treatment

2.4.2. Pharmacokinetics

PK data on idebenone were available from 4 Phase I clinical trials; studies SNT-I-001, SNT-I-002, SNT-I-003 and SNT-I-004. Two studies (SNT-I-002, SNT-I-004) were single-dose studies performed to characterise the PK of Raxone over a seven-fold dose range (150 mg to 1050 mg idebenone). A third study (SNT-I-003) investigated the PK profile following a single oral dose and after repeated three times daily (t.i.d.) oral dosing for 2 weeks. In SNT-I-003, the urinary excretion of idebenone as well as the plasma PK and its metabolites were assessed. This study was performed at two different dose levels (150 mg t.i.d. and 750 mg t.i.d.). In the fourth study (SNT-I-001), the effect of a high-fat meal on the PK of idebenone given as a single tablet of 150 mg and as five tablets of 150 mg was investigated.

All methods used for the analyses of idebenone and its metabolites in plasma as well as urine have been adequately validated and could therefore be considered reliable with regards to accuracy and precision of quantification of the analytes using LC-MS/MS. As the available analytical techniques did not allow to measure conjugated idebenone and its metabolites, samples were subjected to enzymatic acid hydrolysis prior to quantification, so that the determined analyte concentration represent the sum of the unconjugated and conjugated molecules. PK parameters were calculated by using non-compartmental methods. Standard statistical methods were applied.

Limited plasma samples were also collected in the pivotal Phase II trial RHODOS in patients with LHON and in two studies conducted in patients with FRDA.

Furthermore, a Population PK (PPK) model has been developed for idebenone and its metabolite QS10 from Raxone-treated subjects in the four Phase I safety and PK studies (total 70 healthy subjects), RHODOS in LHON patients (55 patients) and two Phase III efficacy, safety and tolerability studies in FRDA patients (MICONOS, 173 patients and IONIA, 46 patients). A non-linear mixed-effect modeling approach was use with one- or two- compartmental models as a starting point for each PK model. A full covariate model approach was implemented, where all covariate-parameter relationships of interest and significance following a univariate analysis were entered in the model, and parameters were estimated. The full model was further reduced to identify the final model based on various goodness-of-fit criteria. The idebenone plasma concentration-time data was adequately described by a one-compartment model with first-order absorption and elimination.

The Applicant also performed two *in vitro* studies to assess the effects of idebenone and QS10, on the inhibition of Cytochrome P450 CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 isoenzymes as well as the potential for induction of CYP1A2, CYP2B6 and CYP3A4 (with the measurement of mRNA) in human primary hepatocytes. Furthermore, the ability of idebenone to act as a substrate or inhibitor of P-glycoprotein (P-gp) was assessed.

Absorption

Single dose studies showed that, when only one dose of idebenone was administered, plasma concentrations of idebenone were mostly below the limit of quantification. Between-subject variability of

plasma idebenone concentrations was relatively high (coefficient of variance of AUC_{0-t} and C_{max} was 44 to 124%).

After administration of repeat doses in fasting conditions, time to reach maximum plasma concentration (t_{max}) of unconjugated and total idebenone was reached rapidly, with a median (range) of approximately 0.67 (0.33-2.00) hours and 1.33 (0.67-2.67) hours respectively. The corresponding figures after administration of a high-fat meal were 1.17 (0.67-3.50) and 1.33 (1.00-3.00) hours. The data provided thus indicate that food modifies the bioavailability of idebenone with a 5-fold increase in the maximum plasma concentration (c_{max}) and a 7-fold increase in the area under the curev ($AUC_{0-\infty}$) when idebenone was given in fed conditions.

No bioequivalence studies have been performed since the final formulations were used in most of the clinical pharmacology studies as well as in the pivotal efficacy and safety study. Absolute bioavailability of idebenone has not been studied given that it has not been administered intravenously.

Distribution

No data on distribution in humans have been submitted. A summary of data from the scientific literature for *in vitro* and animal studies have been provided (see section 2.3.3.). In addition, the Applicant referred to the reference product Mnesis, which was considered acceptable by the CHMP (see also section 2.1. type of Application and aspects on development). As per the product information of Mnesis, idebenone passes the blood-brain barrier and is distributed at significant concentrations in cerebral tissue.

Elimination

Following oral administration, idebenone is rapidly metabolised via oxidative shortening to yield metabolites QS10, QS6 and QS4. Idebenone and these metabolites concomitantly undergo conjugation via glucuronidation and sulphatation to yield conjugated moieties. These are represented by IDE-C (IDE-C), QS10-C, QS6-C and QS4-C.

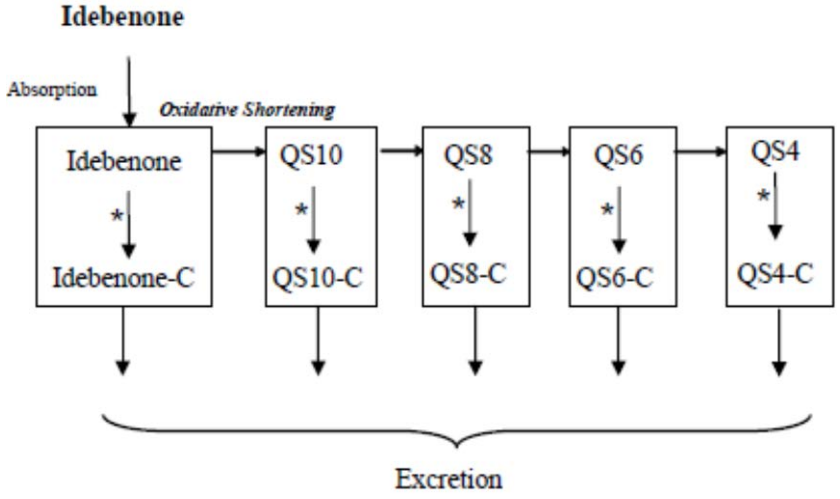


Figure 1 – Metabolism of idebenone

* conjugation

Accordingly, systemic exposure to idebenone was generally low compared to its metabolites suggesting extensive first-pass elimination. Plasma concentrations of idebenone were measured, in general, between approximately 0.33 and 2.67h post-dose and 0.33 to 6h post-dose after single and repeated

administration of 150 and 750 mg Raxone, respectively. There was no excessive accumulation of idebenone in plasma, consistent with a short half-life relative to the dosing interval.

In the single and repeat dose study, QS4+QS4-C was the most prominent drug-derived material in urine, representing, on average, 49.3 to 68.3 % of the total amount of drug administered. QS6+QS6-C represented 6.45 to 9.76 %, whereas the amount of QS10+QS10-C and idebenone+idebenone-C was close to 1% or below. No meaningful determinations of the apparent terminal half-life ($t_{½}$) and $AUC_{0-\infty}$ were possible from the limited measurable concentrations.

Dose proportionality and time dependencies

The pharmacokinetics of total idebenone and its related metabolites has been shown to be dose and time proportional for doses between 150 mg t.i.d. and 750 mg t.i.d. Following a doubling in dose, systemic exposure (AUC and c_{max}) increased, on average, approximately 1.7 to 2.5-fold. For unconjugated idebenone, the data did not allow any assessment of time dependency since $AUC_{0-\infty}$ could not be determined after a single dose.

The consequences of possible genetic polymorphism have not been evaluated. However, this missing information is also true for the reference product Mnesis.

Limited PK information was available in the target population. In LHON patients, the highest mean plasma exposure following administration of 300 mg idebenone t.i.d. was 3.18 ng/ml. In comparison, in FRDA patients receiving doses up to 750 mg t.i.d., the highest measured exposure to idebenone was 42.5 ng/ml in study week 52 (MICONOS study) and mean exposures in the high dose group were 4.261 ng/ml. The highest mean exposures were measured in the IONIA trial at 750 mg t.i.d. in week 4 (7.547 ng/ml). Thus, exposure to idebenone in LHON patients in RHODOS was lower than in the other two FRDA Phase III trials.

Special populations

The Applicant provided results from a population PK model, in which age, race, body mass index, body weight, health status (healthy subjects, LHON patients and FRDA patients), food effect, creatinine clearance, transaminases, bilirubin and disease severity were incorporated as covariates. Of these covariates, only food (see also results for absorption above) and body weight were considered relevant factors. However, although the inclusion of weight as a covariate effect on clearance (CL/F) was statistically significant, it accounted for only a very small proportion of the high inter-individual variability observed. When CL/F was adjusted for body weight there was only a small reduction in variability (55 to 52 %).

No data were provided for renal and hepatic impaired subject, but creatinine clearance was investigated as a covariant in the PPK model and no statistically significant was found.

Raxone has not been studied in children under 14 years or in the elderly.

Pharmacokinetic interaction studies

No *in vivo* interaction studies have been performed for LHON patients.

Pharmacokinetics using human biomaterials

In order to investigated the potential inhibitory effects of idebenone and QS10 on human CYP450 isoenzymes, metabolism of the model substrates phenacetin (CYP1A2), bupropion (CYP2B6), paclitaxel (CYP2C8), tolbutamide (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6), midazolam/testosterone (CYP3A4), was measured *in vitro* in human liver microsomes, in the presence of

idebenone or QS10 at concentrations ranging from 0.65 – 96 µM. Positive control inhibitors were used to assess the responsiveness of the test system. Ki data were used in conjunction with the maximum plasma concentrations observed *in vivo* to calculate the magnitude of a potential interaction. The data indicated that inhibition of human CYP450 isoenzymes occurs in the mid-micro molar range of idebenone and QS10 which was significantly much higher than the positive controls used in the study. Furthermore, binding to human plasma proteins was measured for idebenone and QS10 and recorded as 98.5% and 98.8% respectively.

The potential of idebenone and QS10 to induce CYP1A/1A2, CYP2B6 and CYP3A4 was assessed in fresh human hepatocytes from 3 individual donors at three concentrations (0.1, 1 and 10 µM). Induction was evaluated using both catalytic activity and mRNA endpoints. The only statistically significant increase in activity induced by idenebone was observed at 10µM for CYP2B6, with a maximum increase of 1.3-fold, which was 10.0% of the activity observed with the control inducer phenobarbital.

The Applicant furthermore investigated the ability of idebenone to act as a substrate or inhibitor of P-gp. At concentrations of 0.1 µM, 1 µM, 10 µM and 100 µM, no efflux of idebenone was observed in the MDR1-MDCK cell line. However, idebenone inhibited P-gp activity, as measured by the ability to inhibit the efflux of the established P-gp substrate loperamide, with IC_{50} values of approximately 50 µM. As intestinal exposure in clinical practice will result in 7-fold higher concentrations than the IC_{50}, inhibition of P-gp could not be ruled out.

2.4.3. Pharmacodynamics

No pharmacodynamic studies have been conducted with Raxone in humans.

The pharmacodynamic effects of idebenone have been studied in three studies using a mouse model as well as in cell culture experiments using the retinal ganglion cell line RGC-5 as described in section 2.3.2. When applying conversions for the calculation of the human equivalent dose, the estimates suggest that the concentration that could be reached in the human eye is comparable to the concentrations that showed efficacy *in vitro*.

2.4.4. Discussion on clinical pharmacology

Information on pharmacokinetics has been acquired from 4 Phase I clinical pharmacology studies, three Phase II and III studies in LHON (RHODOS) and FRDA (MICONOS and IONIA) patients and from a Population PK model for both idebenone and its metabolite QS10, generated from all studies mentioned before. Reference was also made to the reference product Mnesis, which was considered acceptable by the CHMP (see also section 2.1. type of Application and aspects on development).

After oral administration, idebenone is rapidly absorbed and shows considerable inter-subject variability after single or repeated doses. Intake of food significantly increased the absorption rate, causing an increase in exposure. The pivotal trials were conducted in fed conditions and the intake of idebenone is recommended with food, as reflected in the SmPC.

Idebenone is quickly cleared from the blood by first pass metabolism. It is metabolised via oxidative shortening of the side chain to QS10, QS6, QS8 and QS4, resulting in low plasma concentrations of unchanged idebenone relative to its metabolites. Both idebenone and its metabolites are conjugated before excretion. The metabolites behave dose-proportional like the parent compound with linear PK profiles.

Effects on special populations were examined in a population PK model for idebenone and its metabolite QS10. Besides the already known food effect and a small effect of body weight, none of the other covariantes tested, i.e. age, gender, race, dose, body mass index, health status, creatinine clearance, transaminases, bilirubin and disease severity, were found to considerably affect PK parameters. As the effect of body weight only seemed to represent a small percentage of the large inter-individual variability observed, the CHMP agreed that no dose adjustment based on weight was needed.

No data were provided for renal and hepatic impaired subjects, and therefore the CHMP agreed that healthcare professionals should be advised to exercise caution when prescribing Raxone in this population.

To address the missing data for children < 14 years, the Applicant proposed restricting the indication to use in patients of 14 years of age and older. However, the CHMP considered that LHON may also occur earlier during childhood (see also discussions on clinical efficacy in section 2.5.5.). Nevertheless, safety data in children under 14 years of age should be considered as missing information in the risk management plan (RMP). Safety and effectiveness data will be collected in this population in the planned Product Exposure Registry. Some safety data were also available in FRDA patients as young as 8 years of age, at weight adjusted doses of up to 2250 mg/day.

With regards to older patients, the CHMP noted that the age of onset of LHON's disease is usually low (18 to 30 years of age) and there are only very few LHON patients above 60 years of age. However, although rare, LHON may occur in the elderly and therefore, Raxone may also be administered to older patients. Considering that factors such as age, body mass index or renal function did not appear to significantly affect PK parameters, the CHMP agreed that no specific dose adjustment was warranted in the elderly population, despite the lack of data for this population.

Data from *in vitro* studies showed that idebenone and its metabolite QS10 did not exert systemic inhibition nor induction of CYP450 isoenzymes at clinically relevant concentrations. Furthermore, while idebenone was not a substrate of P-gp in *in vitro* assays, it did inhibit P-gp activity at concentrations that might be reached in the gastrointestinal tract after oral administration. However, no interaction studies in humans have been performed with idebenone. Therefore, and since the available *in vitro* data did not allow prediction of pre-systemic interactions from intestinal CYP450 interaction, a concern remained that idebenone may have an effect on CYP3A4 substrates. The Applicant proposed to conduct a Phase I open label study of the potential PK interaction of idebenone and QS10 with midazolam in healthy male volunteers, to which the CHMP agreed. Furthermore, SmPC section 4.5 was updated with information from the *in vitro* studies and a statement to inform healthcare professionals about the lack of data for pre-systemic inhibition of CYP3A4 and to recommend not to combine Raxone with CYP3A4 substrates.

Information on the mode of action was mainly derived from published *in vitro* and pre-clinical *in vivo* studies using mice LOHN models. No secondary pharmacodynamic studies have been submitted with this Application. Further confirmation on the effect of idebenone in LHON will thus need to be based on the results of the pivotal Phase II trial RHODOS.

Overall, the CHMP was of the view that all relevant clinical pharmacology data were correctly reflected in the product information.

2.4.5. Conclusions on clinical pharmacology

The CHMP considered that the available clinical pharmacology data were suitable to support the Application for a marketing authorisation of Raxone in the treatment of LHON. The product information adequately reflected relevant pharmacology data, including the recommendation to administer Raxone

with food to increase exposure as well as information on the inhibitory effect on P-gp and lack of data for pre-systemic inhibition of CYP3A4.

However, to address the lack of clinical *in vivo* interaction studies and consequently concerns of possible pre-systemic interactions with CYP3A4 substrates, the CHMP considered that the following measure was necessary and thus included as a requirement in the RMP:

Phase I open label study of the potential pharmacokinetic interaction of idebenone (150 mg film-coated tablet) with midazolam in healthy male volunteers.

2.5. Clinical efficacy

The main support for efficacy of Raxone in the treatment of LHON's disease was provided by the pivotal Phase II study SNT-II-003 (RHODOS). Result from RHODOS were further supported by the single visit observational follow-up study SNT-II-003-OFU (RHODOS-OFU) and data gained from an Expanded Access Programme (EAP, SNT-EAP-001). The Applicant furthermore gathered data in form of a historical case record survey (CRS, SNT–IR–006) and made reference to the published literature (Carelli et al., 2011; Mashima et al., 2000; etc).

2.5.1. Dose response study(ies)

No dose response studies were performed by the Applicant. Reports from published studies in LHON patients (Carelli et al., 2011 and Mashima et al., 2000) referred to doses in a range of 180-675mg/day. Data from animal studies suggest that 300 mg t.i.d. may give aqueous humour levels in humans in the range where idebenone prevented ganglion cell death in the non-clinical models (see also section 2.3.). Furthermore, previous studies in patients with FRDA showed that there was no additional benefit at doses of 2250 mg/day over 900 mg/day.

Taking into account the available data at the time, the Applicant assumed that a dose of 900 mg/day would be likely to be both well tolerated and adequate for efficacy testing and hence selected this dose to be administered in three equally divided doses t.i.d. for the pivotal phase II trial.

2.5.2. Main study

Study SNT-II-003 (RHODOS): A double-blind, randomised, placebo-controlled study of the efficacy, safety and tolerability of idebenone in the treatment of patients with Leber's Hereditary Optic Neuropathy

The RHODOS study was initially intended as an exploratory trial, but due to the difficulties in recruiting patients with LHON's disease the study was amended to be used as a "pivotal" confirmative trial supportive of the marketing authorisation of the product.

The Applicant provided both the original study report as well as a revised report based on a re-analysis using a modified intent-to-treat (mITT) population which excluded one patient (patient 23), who was allocated to the placebo arm and experienced a marked spontaneous recovery in vision. Consequently, patient 23 was considered by the Applicant to be natural history confounder.

Methods

RHODOS was a double-blind, randomised, placebo-controlled, parallel group study in LHON patients performed in three centres, in Munich (Germany), Newcastle (United Kingdom) and Montreal (Canada).

Patients were randomised to treatment with either idebenone 900 mg/day or placebo for a period of 24 weeks. A follow-up visit was performed 28 to 35 days after drug discontinuation.

Patients attended the clinic for six out-patient visits: a Screening Visit performed within 4 weeks of randomisation, the randomisation/Baseline visit (Visit 2), Visit 3 after 4 weeks of treatment, Visit 4 after 12 weeks of treatment, Visit 5 after 24 weeks of treatment when study medication was discontinued, and Visit 6 (28 to 35 days after drug discontinuation). Throughout the 24-week treatment period, patients completed a Patient Diary.

Study Participants

Inclusion Criteria

Patients were included in the study if all of the following inclusion criteria were met at Screening (Visit 1) and were confirmed at Baseline (Visit 2):

1. Age ≥14 years and < 65 years.

2. Impaired VA in at least one eye due to LHON.

3. Onset of visual loss due to LHON was 5 years or less prior to Baseline.

4. Confirmation of either G11778A, T14484C or G3460A LHON mtDNA mutations at >60% in blood.

5. No explanation for the visual failure besides LHON.

6. Body weight ≥45 kg.

7. Negative urine pregnancy test at Screening and at Baseline (women of childbearing potential).

Exclusion Criteria

Patients were not included in the study if one or more of the following exclusion criteria were met at Screening (Visit 1) or Baseline (Visit 2):

1. Treatment with Coenzyme Q10 or idebenone within 1 month prior to Baseline.

2. Pregnancy and/or breast-feeding.

3. Weekly alcohol intake 35 units (men) or 24 units (women).

4. Current drug abuse.

5. Clinically significant abnormalities of clinical haematology or biochemistry including, but not limited to, elevations greater than 2 times the upper limit of normal of aspartate aminotransferase (AST), alanine aminotransferase (ALT) or creatinine.

6. Participation in another clinical trial of any investigational drug within 3 months prior to Baseline.

7. Other factor that, in the investigator's opinion, excluded the patient from entering the study.

Patients meeting any of the following criteria at any time during the study were to be withdrawn from the study:

- Use of any investigational drug other than the study medication during the study period
- Pregnancy
- Any other significant medical condition

In addition, each patient had the right to withdraw from the trial at any time for any reason without affecting the right to treatment by the investigator. The investigator also had the right to withdraw the patient if he judged it in the patient's best medical interest.

Treatments

Patients were randomly assigned to treatment with either idebenone or placebo in a 2:1 ratio.

Idebenone (2 x 150 mg tablets) or placebo were to be administered orally t.i.d. with food beginning the morning after the day of Visit 2 (Baseline) and continuing for 6 months (up to Week 24/Visit 5). The total daily dose of idebenone was 900 mg.

Objectives

Primary Objective

- To determine whether administration of idebenone can improve visual function in patients with LHON.

Secondary Objectives

- In LHON patients entering the trial with an eye still less affected than 0.5 logMAR, to determine whether administration of idebenone can mitigate further visual loss in that eye;
- To assess changes in Clinical Global Impression of Change (CGIC) and in Health-Related Quality of Life (HRQoL);
- To assess safety and tolerability following 24 weeks' treatment with idebenone;
- To explore any relationship between retinal nerve fiber layer thickness and LHON and its treatment with placebo and idebenone in both eyes;
- To explore any relationship between colour contrast sensitivity and LHON and its treatment with placebo and idebenone in both eyes (in a subset of patients);
- To explore the relationship between plasma levels of idebenone and measures of efficacy and safety.

Outcomes/endpoints

<u>Primary endpoint</u>

- *Best Recovery* of logMAR VA between Baseline and Week 24 in either right or left eye

<u>Main secondary endpoint</u>

- Best VA: *Best VA* at Week 24 (best eye at Week 24) compared to *Best VA* at Baseline (best eye at Baseline)

<u>Other secondary endpoints</u>

- Count of eyes/patients for which the visual acuity improves (at least 0.2 logMAR) between Baseline and Week 24
- Change in VA between Baseline and Week 24 of the patient's best eye at Baseline
- LogMAR VA as a continuous variable in both eyes

- In LHON patients with an eye ≤0.5 logMAR at Baseline, the proportion of patients in which the VA in the initially least affected eye does not deteriorate to 1.0 logMAR or more
- Change in scotoma area as assessed by Humphrey™ 24:2 visual field analysis in both eyes, as a continuous variable
- Change in retinal nerve fiber layer thickness as a continuous variable in both eyes
- Change in colour contrast sensitivity as a continuous variable in both eyes (in a subset of patients)
- logMAR VA as a continuous variable in both eyes
- CGIC change from Baseline at Week 12 and Week 24
- Change in HRQoL assessed by VF-14 questionnaire
- Change in self-reported general energy levels assessed by Visual Analog Scale (VAS) from Baseline to Week 24
- Plasma levels of idebenone matched to measures of efficacy and safety

Endpoints included post-hoc with the revised study report

- Proportion of patients with improvement in primary endpoint and main secondary endpoint
- Proportion of patients with clinically relevant recovery from Baseline (improvement of at least logMAR 0.2 for patients with “on-chart” VA at Baseline, or an improvement from “off-chart” VA to at least logMAR 1.6 for patients with off-chart VA at Baseline)
- Proportion of eyes with a clinically relevant recovery from Baseline
- Proportion of patients with a clinically relevant worsening (CRW)
- Effect size of changes in patients with clinically relevant recovery
- Proportion of patients in whom the Recovery observed improved the patient's Best VA
- Proportion of patients presenting with clinically relevant recovery from the VA nadir (the worst VA at any time post-Baseline)
- Proportion of eyes with clinically relevant recovery from the VA nadir
- The time to clinically relevant VA recovery

Measurements of VA

VA, expressed as logMAR values, was assessed using ETDRS (Early Treatment Diabetic Retinopathy Study) charts. Using the logMAR scale allows quantification of results over a large range of visual abilities from 0.0 (normal vision) up to 1.68 (able to read only one large letter correctly at one meter).

“On Chart VA” was distinguished from “Off Chart VA” as follows:

- If the patient is able to read letters on the chart, “On Chart VA” was measured.
- If the patient could not read any letters (being off the logMAR scale), the investigator recorded whether the “Off Chart VA” was reduced to counting fingers (CF) from a distance of 30 cm, hand motion (HM) or light perception (LP) = semi-quantitative results.

For patients with very poor vision, the assignment of a value of logMAR 0.3 for each step in the categorical scale was used in the primary efficacy analysis, i.e. for CF a score of logMAR 2.0 was attributed, for HM a score of logMAR 2.3 was attributed and for LP a score of logMAR 2.6 was attributed.

VA in both eyes was assessed at Screening, Baseline/Visit 2 and Visits 3, 4, 5 and 6. When measuring acuity in the right eye, the left eye was covered (and vice versa). Only one reading of a given letter was allowed. The distance to the chart was 4 meters. If, however, at least 20 letters were not read correctly from 4 meters, the patient's distance to the chart was reduced to 1 meter and the logMAR score obtained reading the 1 meter rows. The distance to the chart was 4 meters. If, however, at least 20 letters were not read correctly from 4 meters, the patient's distance to the chart was reduced to 1 meter and the logMAR score obtained reading the 1 meter rows.

A patient's VA at nadir (the worst VA at any time post-Baseline) was only considered worse than the VA at Baseline if the worsening observed post-Baseline was clinically relevant. Any eye that deteriorated from reading at least 5 letters "on-chart" (equivalent to 1 full chart line) to "off-chart" VA, or which deteriorated "on-chart" by at least 10 letters (equivalent to 2 chart lines), was considered to have deteriorated by a clinically relevant degree and therefore to have reached nadir post-Baseline.

Sample size

The sample size of 84 patients for this study was estimated based on the following assumptions for patients in the ITT population: VA change of –0.05 ± 0.3 logMAR in the placebo group and –0.25 ± 0.3 logMAR in the idebenone group. Such a difference is considered relevant from a clinical point of view. Under these assumptions and with the proportion of patients receiving idebenone and placebo of 2:1 respectively, 84 patients provide 80% statistical power to reject the null hypothesis of no difference in VA change between the two groups. The calculation was based on a two-sided unpaired t-test at the 5% significance level, i.e., it was performed under the additional assumption that the stratification factors do not influence the outcomes.

Randomisation

After establishment of eligibility, patients were randomly assigned to a treatment arm in the proportion 2:1 (idebenone: placebo). Randomisation was stratified by disease history (onset more or onset less than one year prior to randomization) and by mutation type (G11778A, G3460A and T14484C), to ensure balanced treatment allocation within the six resulting strata. The randomisation procedure was centralised. For each of the six strata a computer-generated randomisation list was created with blocks containing idebenone and placebo allocations in the correct proportion but in random order. The block size was 6.

Blinding (masking)

The patient and any persons involved in the conduct of the study (investigators and their site staff, monitors and sponsor) were blinded to the treatment. Unblinding of a patient's treatment was possible but was only to be done when a medical emergency necessitated identification of the study substance the patient had received. Once a treatment had been unblinded, the patient was not to receive any further study medication and was to be withdrawn from the study.

Statistical methods

For continuous variables the mean, standard deviation (SD), standard error (SE), median, and range were calculated. For discrete variables, the number of values in each category and the percentage in each category were calculated.

Analyses were performed using SAS® version 8.2. For all analyses, p-values were reported as well as two-sided 95% confidence intervals for point estimates. Statistical significance was declared for p-values below 5%. For interaction tests, a two-sided significance level of 10% was used.

Analysis Populations

- Safety Population

The safety population was used for analysis of all safety variables. It included all randomised patients who received at least one dose of the study medication and for whom a safety assessment was available. Patients were analysed according to the treatment actually received.

- ITT population

Analyses of all efficacy variables were performed on the ITT population. This population included all randomised patients who received at least one dose of the study medication. Patients were analysed as randomised regardless of protocol violations.

- mITT Population

The mITT population was the same as the ITT population but for VA and colour contrast analyses excluded Patient 23 (randomised to placebo) identified as a natural history confounder due to on-going spontaneous recovery of vision at the time of randomisation into the study. Patients were analysed as randomised regardless of protocol violations.

- PP population

All patients from the ITT population who had no major protocol deviation were included in the PP population (referred to in the study protocol as 'according to protocol'). In this context, a major protocol deviation was defined as a protocol deviation that was considered to have a major impact on the efficacy results. Major protocol deviations were identified prior to the analysis and before breaking the code. The final decision as to which deviations were major was made based on clinical judgment.

Primary and main secondary efficacy analysis

The primary efficacy analysis was performed on the ITT population and repeated as a secondary analysis on the PP population. Missing data were handled using a Mixed-Model Repeated Measures (MMRM) (see Section 11.4.2.2). The between-group difference in the primary efficacy variable was analysed using a repeated measures analysis of covariance (ANCOVA) model with baseline values used as covariate and treatment group, mutation type and disease history as fixed factors. In addition, the visit and visit*treatment interaction were included in this model as fixed factors.

Three further analyses which did not require data imputation using MMRM were performed for the primary efficacy endpoint using three different strategies for handling missing data. In these analyses, missing values were either imputed with a mean of the available post-baseline visits, imputed using last observation carried forward (LOCF), or only used available data. In addition, exploratory sensitivity analyses were performed using the best case scenario (the best available efficacy variable from any post-Baseline visit was used to impute missing data) and worst case scenario (the worst available efficacy variable from any post-Baseline visit was used to impute missing data). In these sensitivity analyses, the primary endpoint was analysed using an ANCOVA model with baseline values used as covariate and treatment group, mutation type and disease history as fixed factor.

If Baseline or demographic characteristics with prognostic factors were very unbalanced between treatment groups, further models including such variables or subgroups of patients were to be analysed

at the discretion of the study statistician. Furthermore, the interactions between these subgroup factors with treatment group were to be investigated.

Other efficacy analysis

Analysis of the other secondary efficacy variables was performed using the ITT population.

Sensitivity analyses

Patients with very poor vision will not have a quantifiable acuity score, that is, they are off the logMAR scale. The study protocol followed the ophthalmological convention for off-chart vision. However, using another assignment rule to the semi-quantitative results CF, HM and LP may have an effect on the outcome of the study. Therefore, a number of sensitivity analyses were performed on the VA outcomes of the trial, which also served the purpose of demonstrating the robustness of the proposed primary assignment.

Subgroups

Separate analysis of specific subgroups according to

- mutation type
- history of disease onset (≤ 1 year; > 1 year)
- smoking history [has the patient ever smoked (Yes/No), is the patient a current smoker (Yes/No)]

were performed of the primary and selected secondary endpoints. Groups could be pooled if they contained less than 8 patients.

Additional analyses not planned in the original statistical analysis plan

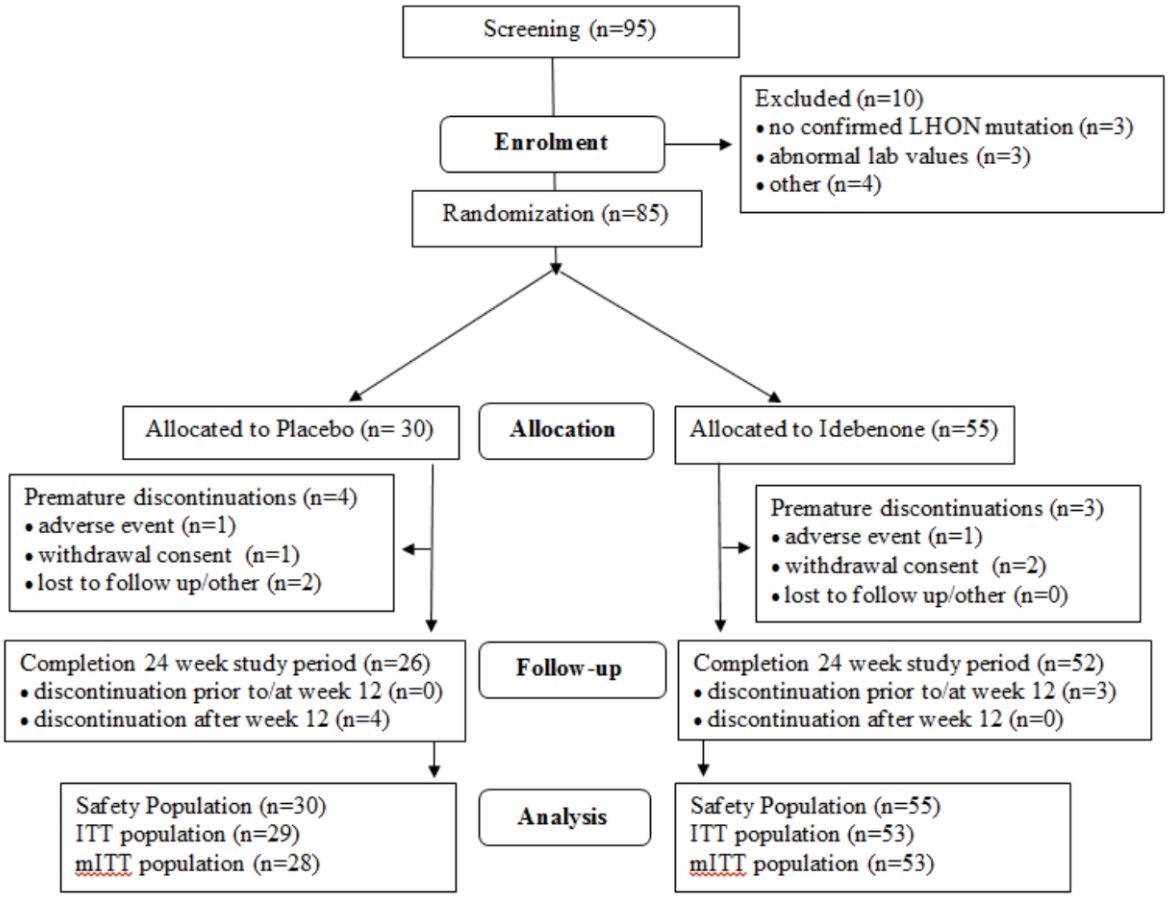
Several additional efficacy analyses were performed post hoc including:

- primary and main secondary endpoints as well as the secondary endpoints 'change in logMAR visual acuity including both eyes and assuming that eyes within a patient are independent' and 'change in visual acuity between Baseline and Week 24 of the patient's best eye at Baseline' for the subgroup of the ITT population excluding patients with mild visual impairment (defined as logMAR <1.0 in both eyes)
- subgroup analyses based on
    - age (<30 years and >30 years)
    - absence or presence of discordant visual acuity at Baseline (defined as patients with at least 2 lines difference in visual acuity (logMAR 0.2) between their left and right eye)

Furthermore, several additional endpoints were included post-hoc with the revised study report, including endpoints using nadir as described above.

Results

Participant flow



A total of 85 patients were randomised to study treatment (44 in Munich, 30 in Newcastle and 11 in Montreal), 55 to idebenone 900 mg/day and 30 to placebo. Three patients (two treated with idebenone and one treated with placebo) were prospectively excluded from the ITT population for the analysis of VA endpoints due to inaccurate recordings in VA measurements either at Baseline or at Visit 5 (Week 24) and thus 53 patients treated with idebenone and 29 patients treated with placebo were included in the ITT population for all VA endpoints. In addition, patient 23 (randomised to placebo) identified as a natural history confounder due to on-going spontaneous recovery of vision at the time of randomisation into the study was excluded in the mITT population.

A total of 7 patients discontinued the study prematurely, 3 patients (5.5%) treated with idebenone and 4 patients (13.3%) treated with placebo. The most commonly reported reason for premature discontinuation was withdrawal of consent (2 patients treated with idebenone and 1 patient treated with placebo). One patient in each treatment group was withdrawn due to adverse events. Finally, two patients in the placebo group were lost to follow-up and discontinued for other reasons, respectively.

A total of 15 patients (12 patients [21.8%] in the idebenone group and 3 patients [10.0%] in the placebo group) had at least one major protocol deviation. The most commonly occurring major protocol deviations were compliance outside 80 to 120% and visual acuity tests not performed according to protocol.

Recruitment

Patients were randomized in three study sites, 44 in Munich, 30 in Newcastle and 11 in Montreal. The first subject was enrolled on 7 April 2007 and the last subject completed the study on 19 February 2010.

Conduct of the study

There were several updates of the study protocol (8 general amendments and 1 site specific amendment) and changes to the originally planned statistical analyses during the course of the study. The main changes are summarised below.

The primary study objective was originally 'to determine whether administration of idebenone in patients with LHON onset within the last 3 months can mitigate visual loss in the initially least affected eye' and the primary endpoint was 'the proportion of patients in whom the initially least affected eye does not deteriorate to >1.0 logMAR at or before Week 36'. Patients were required to present with the worst eye affected >0.5 logMAR and the least affected eye <0.4 logMAR at baseline to ensure a sufficient difference in VA existed between the eyes where natural history would suggest a high probability of deterioration in the least affected eye within the period of the study.

These criteria proved to be extremely difficult to meet and no patients with one affected eye and one as yet unaffected eye meeting the inclusion criterion had been randomised into the trial 12 months after initiation. In Amendment 3 of the protocol, dated 25 July 2007, the primary objective of the trial and the primary endpoint were therefore amended in order to improve recruitment. The requirement for onset of visual loss within 3 months of Baseline was extended to include established disease of five years or less prior to Baseline (stratification for > and ≤ 1 year was introduced) and the exclusion of patients with VA in their least affected eye worse than 0.4 logMAR was correspondingly eliminated. Thus, not only are acutely sick patients were to be enrolled, but also those who are in the post-acute stage and have had affected eyes for up to five years. The primary objective was changed to 'to determine whether the administration of idebenone can improve visual function in LHON' and the primary endpoint was changed to 'best recovery of logMAR visual acuity between Baseline and Week 24 in either the right or left eye'. At this time the previous primary endpoint became secondary as ;in patients entering the trial with an eye still less affected than 0.5 logMAR, proportion of patients in whom the visual acuity in the initially least affected eye does not deteriorate to 1.0 logMAR or more'.

It was furthermore recognised in Amendment 3 that the new best recovery of VA primary endpoint would not necessarily reflect changes in VA relevant to the patient's overall ability to see. Therefore, change in the patient's best logMAR VA between Baseline and Week 24 (where the patient's VA in the better seeing eye at Baseline would be compared to the patient's VA in the better seeing eye at Week 24, even if the better seeing eye was not the same one at Week 24 as at Baseline) was selected as a secondary endpoint to complement the new primary endpoint. This endpoint later (Amendment 8, 14 January 2010) became the key secondary endpoint.

The sample size was increased to 84 patients to account for the more heterogeneous population. The inclusion criteria were modified to include patients from 14 to 65 years instead of 16 to 65 years due to a request from a centre two treat 2 patients below the original age cut-off of 16 years.

Furthermore, the study duration was shortened from 36 weeks to 24 weeks and the patient randomisation ratio changed from 1:1 to 2:1 in favour of idebenone, in an attempt to encourage patients to enrol.

Baseline data

Table 2 provides an overview of the demographics of the RHODOS study population.

Table 2 – Demographic Characteristics (ITT Population[#])

	Idebenone N=55	Placebo N=30	Total N=85
Age (years)			
Mean (SD)	33.8 (14.76)	33.6 (14.58)	33.7 (14.61)
Median	30.0	28.5	30.0
Minimum, maximum	14, 63	14, 66	14, 66
Sex, n, (%)			
Male	47 (85.5)	26 (86.7)	73 (85.9)
Female	8 (14.5)	4 (13.3)	12 (14.1)
Race, n (%)			
Caucasian/white	53 (96.4)	30 (100)	83 (97.6)
Black	1 (1.8)	0	1 (1.2)
Other	1 (1.8)	0	1 (1.2)
Height (cm)			
Mean (SD)	175.64 (8.422)	174.42 (7.050)	175.21 (7.944)
Weight (kg)			
Mean (SD)	74.52 (13.486)	75.78 (13.683)	74.96 (13.488)
BMI (kg/m^2)			
Mean (SD)	24.20 (4.383)	24.92 (4.411)	24.45 (4.381)

The majority of patients (33 patients [60.0%] in the idebenone group and 18 patients [60.0%] in the placebo group) had smoked prior to enrolment and 21 patients (38.2%) in the idebenone group and 13 (43.3%) in the placebo group were currently smoking.

Baseline data for the mtDNA mutation and VA as well as time since onset of symptoms are summarised in Table 3. Only 8 patients at Baseline had at least one eye with a logMAR ≤0.5 (6 patients [10.9%] in the idebenone group and 2 patients [6.7%] in the placebo group. For the ITT population used for visual acuity assessments (n=82), at Baseline mean (SD) visual acuity pooled across both eyes was logMAR 1.75 (0.58) in the idebenone group and logMAR 1.68 (0.54) in the placebo group.

Table 3 – Main Baseline Characteristics including Mutation Status and VA (ITT population)

	Idebenone N=55 (N=53 for VA)	**Placebo N=30 (N=29 for VA)**	**Total N=85 (N=82 for VA)**
mtDNA mutation			
G11778A	37 (67.3)	20 (66.7)	57 (67.1)
T14484C	11 (20.0)	6 (20.0)	17 (20.0)
G3460A	7 (12.7)	4 (13.3)	11 (12.9)
Months since onset of vision loss			

Mean (SD)	22.8 (16.2)	23.7 (16.4)	23.1 (16.2)
Median (Range)	17.8 (3 – 62)	19.2 (2 – 57)	18.2 (2 – 62)
Baseline mean logMAR VA ±SD (including semi-quantitative results for CF, HM, LP)			
Right eye	1.75 (0.584)	1.73 (0.478)	1.75 (0.546)
Range	0.2 – 2.6	0.7 – 2.3	0.2 – 2.6
Left eye	1.76 (0.59)	1.63 (0.600)	1.71 (0.593)
Range	0.2 – 2.6	0.1 – 2.3	0.1 – 2.6
Pooled eyes	1.75 (0.584)	1.68 (0.540)	1.73 (0.569)
Range	0.2 – 2.6	0.1 – 2.3	0.1 – 2.6
Baseline logMAR distribution n (%)			
1 eye logMAR ≥ 1.0	5 (9.4)	2 (6.9)	7 (8.5)
Both eyes logMAR ≥ 1.0	45 (84.9)	25 (86.2)	70 (85.4)
Both eyes logMAR < 1.0	3 (5.7)	2 (6.9)	5 (6.1)
Eyes on or off chart (FC, HM and LP) n (%)			
1 eye off chart	11 (20.8)	3 (10.3)	14 (17.1)
Both eyes off chart	25 (47.2)	13 (44.8)	38 (46.3)
Both eyes on chart	17 (32.1)	13 (44.8)	30 (36.6)

A total of 56 patients (37 [67.3%] in the idebenone group and 19 [63.3%] in the placebo group reported medical histories and continuing medical conditions that were active at the start of the study. The most commonly reported medical conditions were abnormalities of investigations reported by 23.5% of patients (18.2% in the idebenone group and 33.3% in the placebo group) and vascular disorders reported by 22.4% of patients (20.0% in the idebenone group and 26.7% in the placebo group). At the start of the study, the most commonly reported medical condition by preferred term was hypertension in the idebenone group (reported by 20.0% of patients compared with 13.3% in the placebo group). In the placebo group, the most commonly reported medical condition by preferred term was increased gamma-glutamyl transferase (reported by 20.0% of patients compared with 7.3% in the idebenone group).

In both treatment groups, the most commonly used concomitant medications were anilides, mostly paracetamol, which were used by 17 patients (30.9%) in the idebenone group and 10 patients (33.3%) in the placebo group and propionic acid derivatives, mostly ibuprofen, which were used by 7 patients (12.7%) in the idebenone group and 3 patients (10.0%) in the placebo group.

Numbers analysed

Four populations were defined for analysis purposes (see methods for a description).

The *Safety Population* included 85 patients, 55 treated with idebenone and 30 treated with placebo.

The *ITT population* included 82 patients, 53 treated with idebenone (96.4% of those randomised) and 29 treated with placebo (96.7% of those randomised). As explained above, 3 patients were prospectively excluded from the ITT population for all VA analyses.

The *mITT population* was the same as the ITT population used for VA analyses but excluded Patient 23, thus including 81 patients, 53 treated with idebenone (96.4% of those randomised) and 28 treated with placebo (93.3% of those randomised).

The *PP population* was a subset of the ITT/mITT population and included all data from subjects who had no major protocol deviations. In addition, one patient was recorded erroneously as a non-completer and was excluded from the PP population although he completed the study. Thus, the PP population included 65 patients, 41 treated with idebenone (74.5% of those randomised) and 24 treated with placebo (80.0% of those randomised).

Outcomes and estimation

The main results of RHODOS are summarised in this section relevant to the assessment of this Application. Relevant post-hoc analyses are reported under 'ancillary analyses'.

- **Primary endpoint: Best recovery of logMAR VA in either right or left eye**

Base on analyses in the ITT population, patients in the idebenone group improved by logMAR -0.135 (+6 letters) from Baseline to Week 24 whilst patients in the placebo group improved by logMAR -0.071 (+3 letters). The difference between treatments (logMAR -0.064, equivalent to 3 letters) was not statistically significant. Results for both the ITT and the mITT populations are summarised in Table 4.

Table 4 - Best Recovery in VA (ITT and mITT Population)

	Estimated Change (95% CI) [estimated change in letters]		**Estimated Difference ± SEM (95% CI)** [estimated change in letters]	**p-value**
	Raxone	**Placebo**		
ITT population				
N	53	29		
Week 24	-0.135 (-0.216, -0.054) [+6 letters]	-0.071 (-0.176, 0.034) [+3 letters]	-0.064 ± 0.061 (-0.184, 0.055) [3 letters]	0.291
mITT population (excluding patient 23)				
N	53	28		
Week 24	-0.136 (-0.212, -0.060) [+6 letters]	-0.036 (-0.137, -0.065) [+1 letters]	-0.100 ± 0.058 (-0.214, -0.014) [5 letters]	0.0862

Results for the PP population and the sensitivity analyses were consistent with those seen for the (m)ITT population.

- **Key secondary endpoint: Best VA at Week 24 (best eye at Week 24) compared to best VA at Baseline (best eye at Baseline)**

For the main secondary endpoint, change in Best VA, there was a worsening in Best VA between Baseline and Week 24 for patients receiving placebo, while Best VA very slight improved in the Raxone group (Table 5). The difference was only statistically significant in the mITT population.

Table 5 - Best VA (ITT and mITT Population)

	Estimated Change (95% CI) [estimated change in letters]		**Estimated Difference ± SEM (95% CI)** [estimated change in letters]	**p-value**
	Raxone	**Placebo**		
ITT population				
N	53	29		
Week 24	-0.035 (-0.126, 0.055) [+1 letter]	0.085 (-0.032, 0.203) [-4 letters]	-0.120 ± 0.068 (-0.2546, 0.0137) [6 letters]	0.078
mITT population (excluding patient 23)				
N	53	28		
Week 24	-0.037 (-0.123, 0.049) [+1 letter]	0.123 (0.010, 0.237) [-6 letters]	-0.160 ± 0.065 (-0.289, -0.031) [8 letters]	0.015

Results for the PP population were consistent with those seen for the (m)ITT population.

The change over time in Best VA (Week 4, Week 12 and Week 24) is depicted in Figure 2.

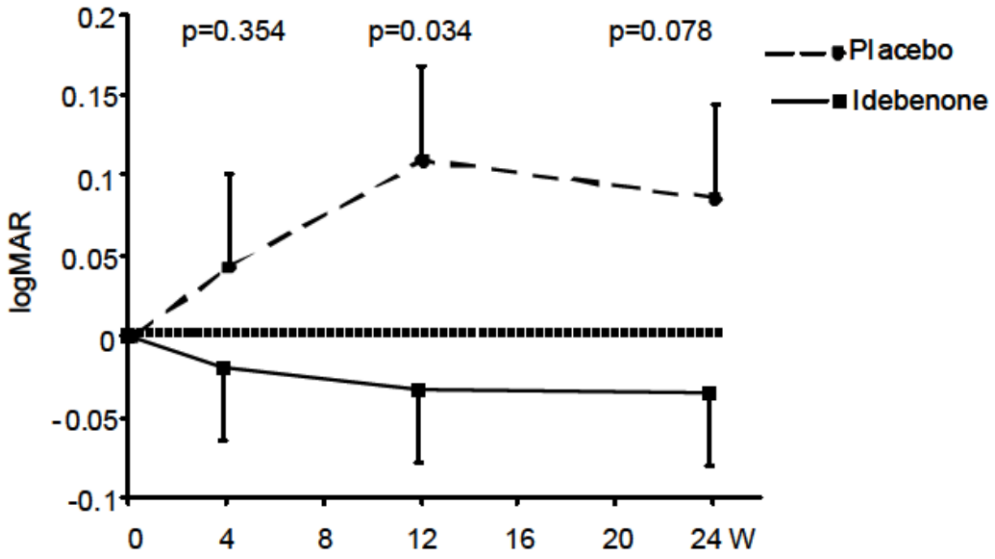


Figure 2 – Change Over Time in Best VA (ITT population)

- **Subgroup analyses for primary and key secondary endpoint**

Several subgroup analyses were pre-defined in the protocol including subgroups by mutation type, disease onset, age and smoker status. Results by mutation type and disease onset for both the primary and the key secondary endpoints are summarised below.

Table 6 – Subgroup analyses for Best Recovery in VA and Best VA by mutation type and onset of disease (ITT and mITT population)

		Estimated Change (95% CI) [estimated change in letters]		Estimated Difference ± SEM (95% CI)	p-value
		Raxone	Placebo		
Primary endpoint: Best recovery in VA					
Mutation type					
G11778A	ITT (idebenone n=35, placebo n=19)	-0.142 (-0.235, -0.049)	-0.153 (-0.180, -0.074)	-0.089±0.079	p=0.259
	mITT (idebenone n=35, placebo n=18)	-0.139 (-0.225, -0.053)	0.009 (-0.111, 0.129)	-0.148±0.073	p=0.047
G3460A (idebenone n=7, placebo n=4)		-0.126 (-0.319, 0.068)	-0.029 (-0.306, 0.248)	-0.097±0.155	p=0.541
T14484C (idebenone n=11, placebo n=6)		-0.096 (-0.260, 0.068)	-0.128 (-0.355, 0.100)	-0.031±0.138	p=0.820
Disease onset					
≥1 year (idebenone n=34, placebo n=19)		-0.193 (-0.290, -0.097)	-0.122 (-0.246, 0.003)	-0.072±0.074	p=0.336
<1 year	ITT (idebenone n=19, placebo n=10)	-0.075 (-0.220, -0.071)	-0.026 (-0.226, 0.175)	-0.049±0.111	p=0.662
	mITT (idebenone n=19, placebo n=9)	-0.093 (-0.213, 0.027)	0.060 (-0.114, 0.234)	-0.154±0.096	p=0.116
Key secondary endpoint: Best VA					
Mutation type					
G11778A	ITT (idebenone n=35, placebo n=19)	-0.045 (-0.148, 0.059)	0.087 (-0.053, 0.228)	-0.132±0.087	p=0.133
	mITT (idebenone n=35, placebo n=18)	-0.045 (-0.141, 0.052)	0.153 (0.018, 0.288)	-0.198±0.083	p=0.019
G3460A (idebenone n=7, placebo n=4)		-0.099 (-0.368, 0.170)	0.239 (-0.146, 0.623)	-0.338±0.211	p=0.128
T14484C (idebenone n=11, placebo n=6)		0.025 (-0.132, 0.182)	-0.039 (-0.255, 0.178)	0.064±0.131	p=0.631
Disease onset					
≥1 year (idebenone n=34, placebo n=19)		-0.127 (-0.218, -0.037)	-0.059 (-0.176, 0.058)	-0.068±0.070	p=0.332
<1 year	ITT (idebenone n=19, placebo n=10)	-0.093 (-0.213, 0.027)	0.278 (-0.001, 0.555)	-0.203±0.153	p=0.190
	mITT (idebenone n=19, placebo n=9)	0.051 (-0.124, 0.227)	0.394 (0.144, 0.643)	-0.342±0.137	p=0.016

- **Selected other secondary endpoints**

Count of eyes/patients for which the visual acuity improves (at least 0.2 logMAR) between Baseline and Week 24

There were a numerically higher proportion of patients/eyes in the idebenone group compared to the placebo group with an improvement in VA of at least logMAR 0.2 at Week 24 compared to Baseline. In analyses on the primary endpoint, 20 out of 53 patients in the idebenone arm had a VA improvement (37.7%) compared to 7 out of 29 patients in the placebo arm (24.1%). The difference of 14% was not statistically significant. Similarly, a difference of 9% between treatment arms for the main secondary endpoint was not significant. As could be expected, the difference between treatment groups was slightly larger when performing the same analyses on the mITT population. An analysis of the proportion of eyes showed a similar trend.

Sensitivity analyses of the proportion of patients showing an improvement in the primary endpoint by change of at least logMAR 0.3 or change of at least logMAR 0.1 was performed. No statistically significant differences were seen between treatments.

In LHON patients with an eye ≤0.5 logMAR at Baseline, the proportion of patients in which the VA in the initially least affected eye does not deteriorate to 1.0 logMAR or more

There were very few patients (N=8) with a least affected eye with logMAR ≤0.5 at Baseline. None of the 6 patients in the idebenone group showed deterioration to logMAR 1.0 or more whereas both patients in the placebo group showed such deterioration. The same results were observed when LOCF was used to impute missing data or when missing values were considered a deterioration.

Other secondary non-VA endpoints

A colour contrast sensitivity test was performed on a subset of patients in one of the study centres. Most patients had abnormal colour contrast sensitivity at Baseline in both Protan (i.e., >6%) and Tritan (i.e., >8%) domains in both eyes (94.9% for Protan and 92.3% for Tritan). For both eyes combined, there was an increase (i.e., worsening) at Week 24 from Baseline in both treatment groups for red-green (Protan) colour confusion which was greater in the placebo group (+5.3%) than in the idebenone group (+1.4%). The difference at Week 24 was -3.9%, which was not statistically significant. No changes from abnormal sensitivity at Baseline to normal (i.e., ≤6%) at Week 24 for any eye for either treatment group was observed. For blue-yellow (Tritan) colour confusion, there was a decrease (i.e., improvement) from Baseline in the idebenone group (-7.2%) and an increase (i.e., worsening) in the placebo group (+6.4%). The difference of -13.6% was statistically significant (p=0.008). Analyses in the mITT population yielded generally larger differences between treatment groups and results for both Protan and Tritan sensitivity were statistically significant. For two eyes in the idenbenone group and one eye in the placebo group with abnormal Tritan sensitivity at Baseline, normal values were achieved at Week 24.

Change in scotoma area was assessed by Humphrey™ 24:2 visual field analysis. However, the interpretation of these visual field data across the entire study population was difficult due to the unreliability of the assessments due to false positive/negative errors and fixation losses.

Changes in retinal nerve fiber layer (RNFL) thickness follows a distinct temporal development, whereby an initial hypertrophy (i.e., increase in RNFL thickness shortly after symptom onset) is followed by a progressive reduction in RNFL thickness (Barboni et al., 2010). To account for this temporal development, RNFL thickness was analysed for patients with ≤6 months, 6-12 months and >12 months of disease history. RNFL thickness in patients with ≤6 months disease history decreased in placebo-treated patients (n=4) over time, whereas patients treated with idebenone (n=6) were protected from this disease-specific loss of RNFL thickness. For patients with 6-12 months disease history and those with >12

months disease history there was very little further loss in RNFL thickness independent of treatment assignment. The small sample size per category did not allow a formal statistical evaluation.

With regards to Health-Related Quality of Life (HRQoL), only small changes in the VF-14 score were observed over the 24-week study period and at Week 24, there was no significant difference between the treatments (estimated mean treatment difference -1.37; 95% CI: -6.25, 3.51; p=0.577).

At Week 24, 12 patients (22.6%) in the idebenone group and 7 patients (24.1%) in the placebo group from the ITT population had an improvement in Clinical Global Impression of Change (CGIC). A total of 43 patients (81.1%) in the idebenone group and 24 patients (82.8%) in the placebo group were experiencing less fatigue or no change in fatigue levels. There was a significant correlation between the change in CGIC and the change in best recovery of VA (primary efficacy endpoint, Spearman's R^2 = -0.32, p = 0.005) and between the CGIC and the change in the Best VA (main secondary endpoint, Spearman's R^2 = -0.34, p = 0.002) for the ITT population. There was no correlation between fatigue score and change in logMAR at Week 24.

At Week 24, patients in both treatment groups reported minimally elevated energy levels assessed by VAS score (0.37 mm for idebenone and 2.17 mm for placebo) with no statistically significant difference between the treatment groups (- 1.80; 95% CI: -11.37, 7.77; p=0.709).

- **Endpoints for post-hoc analyses**

The Applicant presented a number of post-hoc responder analyses, which are summarised below. These analyses were conducted on the mITT population only except for responders with "off-chart" vision at Baseline for who the ITT population was identical to mITT. Re-analyses for some of the responder endpoints were however conducted on the ITT population upon request of the CHMP in order to compare data between different datasets (see section 2.5.4.).

Responder analysis for patients "off chart" at Baseline

Patients who were "off chart" at Baseline comprise a subgroup of severely affected patients who were unable to read any letters on the chart. Amongst this subgroup, 28% of the idebenone treated patients (7 of 25 patients) were able to read at least one full line (5 letters) on chart at Week 24, whilst none of the placebo patients recovered to this level of vision (p=0.0722). Applying the same analysis to all eyes instead of patients resulted in a significant difference between idebenone responders and placebo responders (p=0.0078). The mITT and ITT populations were identical for this endpoint.

Proportion of patients with clinically relevant recovery (CRR) from Baseline

In an attempt to define a clinically relevant definition of responder, a responder analysis was conducted based on the definition for CRR used by Carelli et al. (2011), which distinguished between patients with "on-chart" and "off-chart" vision at Baseline. Using this definition, a significantly higher proportion of patients in the idebenone group (30.2%) than in the placebo group (7.1%) showed CRR from Baseline (p=0.0234; Table 7). Recovery was also investigated in subgroups based on disease duration, mtDNA mutation, age and smoking status.

Table 7 – Proportion of Patients with CRR from Baseline at Week 24 (mITT population)

	Idebenone N=53 n (%)	Placebo N=28 n (%)	p-value[1]
Recovered from Baseline[2] mITT population	16 (30.2)	2 (7.1)	0.0234
Duration of LHON <1 year	4 (21.1)	0	0.2734
Duration of LHON ≥1 year	12 (35.3)	2 (10.5)	0.0596
mtDNA mutation G11778A	11 (31.4)	0	0.0096
mtDNA mutation G3460A	1 (14.3)	0	1.000
mtDNA mutation T14484C	4 (36.4)	2 (33.3)	1.000
Age <30 years	6 (23.1)	0	0.0697
Age ≥30 years	10 (37.0)	2 (15.4)	0.2714
Current smokers	7 (36.8)	2 (16.7)	0.4184
Not current smokers	9 (26.5)	0	0.0428

Last observation carried forward (LOCF) method used for data imputation
1: Calculated using Fisher's exact test
2: Recovery defined as a change of (i) at least logMAR 0.2 from Baseline for patients who had "on-chart" VA at Baseline or (ii) a change from "off-chart" VA to at least logMAR 1.6 for patients who had "off-chart" VA at Baseline

Proportion of patients in whom the observed Recovery from Baseline improved the patient's Best VA and the proportion of eyes with Recovery from Baseline

In 12 out of 16 idebenone-randomised and in 1 out of 2 placebo-randomised patients presenting with CRR, the recovery also improved the patient's best VA.

Recovery was seen in 21 eyes (19.8%) for patients in the idebenone group and in 2 eyes (3.6%) for patients in the placebo group and this difference was statistically significant in favour of idebenone (p=0.0041). Since the total number of patients with a clinically relevant recovery in the idebenone group was 16 patients, this means that 5 patients responded with both eyes.

Effect size in patients presenting with clinically relevant recovery of VA

Table 8 – Treatment Effect Size in Patients Presenting with CRR at Week 24 (mITT population)

	Idebenone N=16 Mean logMAR change (letters)	Placebo N=2 Mean logMar change (letters)
All recoveries	-0.23 (11 letters)	-0.37 (18 letters)

Proportion of patients with clinically relevant worsening (CRW) from Baseline

The proportion of patients with a CRW from Baseline was calculated as the reverse of the recovery i.e., as a change from logMAR ≤1.6 to "off-chart"or a change of logMAR 0.2 "on-chart"). There was no statistically significant difference between the treatments (p=0.6058): CRW was seen in 2 patients (3.8%) in the idebenone group and 2 patients (7.1%) in the placebo group. In the idebenone group one worsening occurred in a patient with the G11778A mutation and one in a patient with the T14484C mutation, and in the placebo group one worsening occurred in a patient with the G11778A mutation and one in a patient with the G3460A mutation.

Proportion of Patients and Eyes with CRR from the VA nadir

Table 9 presents a comparison of the proportions of idebenone- and placebo-randomised patients in the mITT population who recovered from their VA nadir. A statistically significant difference in favour of idebenone was seen for patients presenting with recovery in favour of idebenone (p=0.0321). Statistical significance was also reached in patients with a disease duration ≥1 year, but there was no significant between-treatment difference for disease duration <1 year. Amongst the 3 mtDNA mutations, a significant difference in favour of idebenone was only seen in the subgroup with the G11778A mtDNA mutation. When disease duration and mtDNA mutation were investigated together, only the subgroup of patients with duration of LHON ≥1 year and carrying the G11778A mutation showed a significant difference between treatments in favour of idebenone [9 of 21 patients receiving idebenone (42.9%)versus 0 of 12 patients receiving placebo (0%), p=0.0122].

CRR from VA nadir was seen in 23 eyes (21.7%) for patients in the idebenone group and in 3 eyes (5.4%) for patients in the placebo group. This difference was statistically significant in favour of idebenone (p=0.0066).

Table 9 - Proportion of Patients with CRR from Nadir at Week 24 (mITT population)

	Idebenone N=53 n (%)	Placebo N=28 n (%)	p-value[1]
Recovered from nadir	18 of 53 (34.0)	3 of 28 (10.7)	0.0321
Duration of LHON <1 year	5 of 19 (26.3)	1 of 9 (11.1)	0.6296
Duration of LHON ≥1 year	13 of 34 (38.2)	2 of 19 (10.5)	0.0545
mtDNA mutation G11778A	12 of 35 (34.3)	0 of 18 (0)	0.0044
mtDNA mutation G3460A	1 of 7 (14.3)	0 of 4 (0)	1.0000
mtDNA mutation T14484C	5 of 11 (45.5)	3 of 6 (50.0)	1.0000

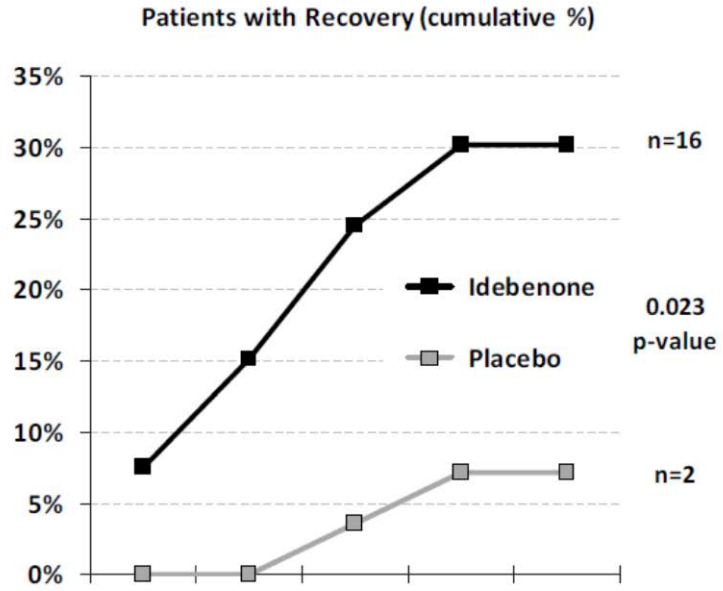
Time to CRR

A logrank test of the difference in the median time to recovery since disease onset in the mITT population between the idebenone-treated (42.4 months) and placebo-treated (median not reached) patients demonstrated a statistically significant difference between the groups (p=0.0133) in favour of idebenone.

Further analysis of the distribution of the recoveries observed as a function of disease duration at Baseline, demonstrates that recoveries were not observed in patients with disease duration greater than 48 months at Baseline. The proportions of recoveries were similar in the ≤12 months, >12-24, >24-36

and >36-48 month baseline disease duration groups. Whilst the number of patients within the >48-60 month Baseline disease duration group was small, this observation suggests that the proportion of recoveries appears to decline with Baseline duration of LHON greater than 48 months.

It is also of interest to note that in both treatment groups the recoveries occurring in patients with the longest Baseline duration of disease occurred in patients carrying the T14484C mtDNA mutation.



Disease Duration Group [months]*	≤ 12	>12 - 24	>24 - 36	>36 -48	> 48	total
Idebenone Recovery (n)	4	4	5	3	0	16
N per Group	19	13	11	5	5	53
Placebo Recovery (n)	0	0	1	1	0	2
N per Group	9	6	5	4	4	28

**Disease Duration at Baseline Assessment*

Figure 3 – Cumulative Percentage of patients Presenting with CRR as a Function of Disease Duration (mITT Population)

Ancillary analyses

Subgroup analyses, sensitivity analyses and post-hoc analyses are described as relevant in the previous section. See section for additional analyses requested by the CHMP for RHODOS, the EAP and/or the CRS.

In addition, upon request by the CHMP requested, the Applicant performed additional analyses including a univariate analysis on responding and non-responding patients to study characteristics potentially prognostic for a response (age at Baseline, gender, mutation carried, time since onset at Baseline and VA differences at Baseline) and to identify potential imbalances in these characteristics that could account for the differences in the proportions of patients responding in the Raxone and placebo groups in RHODOS. The analyses showed a trend towards a higher age at Baseline in responders versus non-responders. In addition, the T14484C mutation was associated with a higher proportion of responding patients, which was expected due to the more benign course of the disease in patients with this mutation. No other prognostic factor has been being identified as influential for the responder rate in this analysis.

The Applicant was furthermore asked to show data for patients classified as responders with regards to improvements on secondary parameters other than VA. In response, reference was made to the CGIC outcome, which correlated significantly with the results of the primary and key secondary endpoints (see results section above). In addition, the Applicant provided analyses on the differences observed in responders and non-responders on Protan and Tritan colour contrast vision, CGIC, VAS for self-assessed energy level and Visual Function VF-14 score. Overall, the results showed numerically better outcomes for these secondary non-VA endpoints for responders compared to non-responders.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present Application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 10 - Summary of efficacy for trial SNT-II-003 (RHODOS)

Title: A double-blind, randomized, placebo-controlled study of the efficacy, safety and tolerability of idebenone in the treatment of patients with Leber's Hereditary Optic Neuropathy (LHON)			
Study identifier	SNT-II-003 (RHODOS)		
Design	Randomised, placebo-controlled, double-blind parallel group study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks not applicable (screening 4 weeks prior to baseline visit) Open Label Follow-Up Single Visit: Mean time from Week 24 of SNTII-003: 30 months
Hypothesis	Superiority of idebenone 900mg/day over placebo in improving visual function of LHON patients		
Treatments groups	Idebenone		Idebenone 900 mg/day (2x150 mg orally 3 times daily), 55 patients enrolled, 24 weeks of treatment
	Placebo		Placebo, 30 patients enrolled, 24 weeks of treatment
Endpoints and definitions	Primary endpoint	Best Recovery in VA	Best recovery of logMAR VA at Week 24 in either right or left eye (whichever shows best improvement) compared to Baseline
	Main Secondary endpoint	Change in Best VA	Best VA at Week 24 (best eye at Week 24) compared to best VA at Baseline (best eye at Baseline)
	Other Secondary endpoint	<u>Responder analysis (A):</u> Proportion of patients with VA deterioration to ≥1.0 logMAR	In LHON patients entering the trial with an eye still less affected than 0.5 logMAR: Proportion of patients in which the visual acuity in the initially least affected eye deteriorates to 1.0 logMAR or more
	Other Secondary endpoint	<u>Responder Analysis (B):</u> Proportion of patient/eyes with ≥0.2 logMAR VA improvement	Count of eyes/patients for which VA improves between Baseline and Week 24 by at least 0.2 logMAR

	Other endpoint *(post-hoc, mITT population only)*	Responder Analysis (C): Proportion of patient/eyes CRR from baseline	Proportion of patients with CRR from Baseline (improvement of at least logMAR 0.2 for patients with "on-chart" VA at Baseline, or an improvement from "off-chart" VA to at least logMAR 1.6 for patients with off-chart VA at Baseline)
	Other endpoint *(post-hoc, mITT population only)*	Responder Analysis (D): Proportion of patient/eyes with CRR from nadir	Proportion of patients with CRR from nadir (the worst VA at any time post-Baseline)
Database lock	28 May 2010		

Results and Analysis

Analysis description	**Primary Analysis**
	The **ITT** population included all randomised patients who received at least one dose of the study medication. Three randomised patients were excluded prospectively from the ITT population for all VA analyses due to apparent inaccurate recordings in VA measurements either at Baseline or at Week 24. The **mITT** population was the same as the ITT population used for VA analyses but excluded Patient 23 (randomised to placebo) identified as a natural history confounder. Results are shown for both ITT and mITT population, where available. For some analyses the ITT and mITT population were identical.

Descriptive statistics and estimate variability

Treatment group		**Idebenone 900 mg/day**	**Placebo**
Number of subjects	**ITT**	**53**	**29**
	mITT	**53**	**28**
Best recovery in VA: Δ logMAR (mean; 95% CI)	ITT	-0.135 (-0.216, -0.054)	-0.071 (-0.176, 0.064)
	mITT	-0.136 (-0.212, 0.060)	-0.036 (-0.137, 0.065)
Change in Best VA: Δ logMAR (mean; 95% CI)	ITT	-0.035 (-0.126, 0.055)	0.085 (-0.032, 0.203)
	mITT	-0.037 (-0.123, 0.049)	0.123 (0.010, 0.237)
Responder analysis (A): Number of patients with VA deterioration to ≥1.0 logMAR out of total (%)	ITT/ mITT	0 of 6 (0%)	2 of 2 (100%)
Responder Analysis (B): Number of eyes/patients with ≥0.2 logMAR VA improvement out of total (%)	ITT	20 of 53 patients (37.7%) 30 of 106 eyes (28.3%)	7 of 29 patients (24.1%) 10 of 56 eyes (17.2%)
	mITT	Same as ITT	6 of 28 patients (21.4%) 8 of 56 eyes (14.3%)
Responder Analysis (C): Number of patients with CRR from baseline (%)	mITT	16 (30.2%)	2 (7.1%)

	Responder Analysis (D): Number of patients with CRR from nadir (%)	mITT	18 (34.0)	3 (10.7)
Effect estimate per comparison Idebenone group vs. Placebo group	Primary endpoint: Best recovery in VA		Δ logMAR estimated (means ± SE)	ITT: -0.064 ± 0.061 mITT: -0.100 ± 0.058
			P-value	ITT: 0.291 mITT: 0.086
	Main secondary endpoint: Change in Best VA		Δ logMAR estimated (means ± SE)	ITT: -0.120 ± 0.068 mITT: -0.160 ± 0.065
			P-value	ITT: 0.078 mITT: 0.015
	Secondary endpoint: Responder analysis (A) Proportion of patients with VA deterioration to ≥1.0 logMAR		P-value	0.036
	Secondary endpoint: Responder Analysis (B) Proportion of patient/eyes with ≥0.2 logMAR VA improvement		P-value - for patients - for eyes	ITT: 0.231; mITT: 0.210 ITT: 0.131; mITT: 0.052
	Post-hoc endpoint: Responder Analysis (C) Proportion of patient/eyes with CRR from baseline		P-value	0.023
	Post-hoc endpoint: Responder Analysis (D) Proportion of patient/eyes with CRR from nadir		P-value	0.0321
Notes	Responder Analyses (C and D) were post-hoc analyses			

2.5.3. Supportive studies

2.5.3.1. RHODOS Observational Follow-Up Study (SNT-II-003-OFU)

This was an observational single-visit follow-up study with the primary objective of examining the change in VA of patients who had previously participated in a double-blind placebo-controlled study of Idebenone (SNT-II-003, RHODOS), and comparing the current VA with that observed at Baseline and after 24 weeks of treatment in RHODOS.

Study participants:

The only inclusion criterion was previous participation in study SNT-II-003 (RHODOS). There were no exclusion criteria.

A total of 60 out of the 85 patients (70.6%) who participated in RHODOS were enrolled into RHODOS-OFU. 41 had previously received idebenone 900 mg/day (74.5% of idebenone-treated patients in SNT-II-003) and 19 had previously received placebo (63.3% of placebo-treated patients in SNT-II-003).

Of the 60 patients, 58 (idebenone: 39 patients; placebo: 19 patients) had been included in the efficacy analysis set. Two patients were not included due to inaccurate VA assessments.

Primary Efficacy Endpoints: Change in best logMAR VA (Best VA) compared to Visit 2/Baseline and Visit 5/Week 24 or last treatment visit of RHODOS.

Secondary Endpoints:

- Change in logMAR VA of individual eyes (Change in VA of Both Eyes) compared to Visit 2/Baseline and Visit 5/Week 24 or last treatment visit of RHODOS.
- Change in logMAR VA of a patient's best eye (Change in VA of the Best Eye) compared to the same eye at Visit 2/Baseline or Visit 5/Week 24 or last treatment visit of RHODOS.
- Change in HRQoL assessed by VF-14 questionnaire compared to Visit 2/Baseline and Visit 5/Week 24 or last treatment visit of RHODOS.

Treatment:

No treatment with idebenone was foreseen in RHODOS-OFU. However, there were 5 patients from the Total Efficacy Population who reported use of idebenone between Week 24 of RHODOS and the RHODOS-OFU visit. The dose used was not provided in all cases, although 3 patients report the use of 900 mg/day.

The influence of idebenone use on the VA outcome was investigated. The Change in Best VA from Week 24 to the SNT-II-003-OFU visit in the Total Efficacy Population was comparable to that seen in the subgroup, in which Idebenone treated patients were excluded.

Results:

The median time of 30 months (range: 20.9 to 42.5 months; 131 weeks) from Week 24 of SNTII-003 to SNT-II-003-OFU was used for illustration purposes in graphs.

The mean (± SD) age of patients recruited was 33.4 (±14.9) years, with a range of 14.0 to 66.0 years. Patients in the Idebenone group were slightly older than those in the placebo group (Mean: 34.4 years versus 31.5 years). The majority of patients recruited were male (50 patients [86.2 %]) and almost all patients (56 patients [96.6 %]) were Caucasian/white. There were 15 patients in the idebenone group and 9 patients in the placebo group with discordant visual acuity (difference in visual acuity of more than logMAR 0.2 between both eyes). VA in the best and worst eye at Baseline as well as the proportion of patients and eyes with "off-label" VA were balanced between treatment groups. The majority of patients had the G11778A mtDNA mutation [28 out of 39 patients (71.8%) in the idebenone arm and 13 out of 19 patients (68.4) in the placebo arm]. Fewer patients had the T14484C (15.4% and 10.5% for the idebenone and the placebo group, respectively) and the G3460A mutation (12.8% and 21.1% for the idebenone and the placebo group, respectively).

A summary of the **mean Change in Best VA** from Baseline of RHODOS to Week 24 and to the RHODOS-OFU visit, and the change from Week 24 to the SNT-II-003-OFU visit are provided in Table 11. Best VA at the RHODOS-OFU visit was slightly worse than at Baseline in patients in the placebo group (mean change in logMAR +0.039, corresponding to a worsening of 1 letter) whereas Best VA improved in the idebenone group (mean change in logMAR -0.134, corresponding to an improvement of 6 letters). Both treatment groups showed almost identical improvements in Best VA between Week 24 of RHODOS and the RHODOS-OFU visit (idebenone: logMAR -0.085, placebo: logMAR 0.088, both equivalent to improvement by 4 letters).

For the **other secondary VA endpoints** (change in VA of Both Eyes and in patient's best eye), broadly similar results were obtained.

Table 11 – Change in Best VA in RHODOS and RHODOS-OFU (Total Efficacy Population)

Change in Best VA	Estimated Change[1] (95% CI) [estimated change in letters]		Estimated Difference[1] ± SEM (95% CI) [difference in letters]	p-value
	Idebenone in SNT-II-003	Placebo in SNT-II-003	Idebenone vs. Placebo	
N	39	19		
BL† to Wk 24†	-0.048 (-0.180, 0.083) [+2 letters]	0.127 (-0.052, 0.306) [-6 letters]	-0.175 ± 0.101 (-0.375, 0.024) [8 letters]	0.0844
BL† to OFU	-0.134 (-0.265, -0.003) [+6 letters]	0.039 (-0.136, 0.215) [-1 letter]	-0.173 ± 0.100 (-0.370, 0.024) [8 letters]	0.0845
Wk 24† to OFU	-0.085 (-0.195, 0.024) [+4 letters]	-0.088 (-0.246, 0.071) [+4 letters]	0.002 ± 0.098 (-0.190, 0.195) [0 letters]	0.9819

1: Data is estimated mean calculated from mixed model for repeat measures (MMRM).

† = study SNT-II-003; OFU = study SNT-II-003-OFU (i.e. this current study, median time since Week 24 was 30 months); BL = Baseline; Wk = week; CI = Confidence Interval; SEM = Standard Error of the Mean.

Semi-quantitative result 1 (logMAR values: CF =2.00; HM=2.30; LP=2.60)

From the 7 patients (12 eyes) in the idebenone group who showed improvement in vision from "off-chart" at Baseline to "on-chart" at Week 24 in RHODOS, long-term follow-up data were available for 5 patients (G11778A or G3460A mutation) from the OFU visit. These 5 patients still had "on-chart" vision at OFU visit. One patient could read only 3 letters, whilst 4 patients still were able to read at least one full line on-chart. Furthermore, 5 additional patients in the idebenone group changed from "off-chart" to "on-chart" vision reading one full line between Week 24 and RHODOS-OFU, resulting in a total of 9 responders. In the RHODOS study at Week 24, no patients/eyes in the placebo group showed improvement from "off-chart" to "on-chart" vision. By the OFU visit, 2 placebo patients (out of 8 for whom data were available) recovered to "on-chart".

VF-14 data were available for 57 patients enrolled in SNT-II-003-OFU. Overall, the changes between VF-14 recorded during RHODOS and RHODOS-OFU were small and differences between idebenone and placebo groups were not statistically significant. There was a small worsening in the idebenone group (-1.7%) compared to a small improvement in the placebo group (2.4%; p=0.205) for the entire period between RHODOS Baseline to RHODOS-OFU

2.5.3.2. Expanded Access Program (EAP)

This EAP (SNT-EAP-001) was established by the Applicant to provide access to Raxone to individual "named" LHON patients at the request and under the personal care of a registered physician according to applicable local regulations. In Europe, Australia and New Zealand, Raxone was provided via a Named Patient Programme. As a secondary objective, in addition to providing access to Raxone to patients, the EAP aimed at collecting any information relevant to the benefit-risk evaluation of Raxone that becomes available in the treatment of LHON. There was no control group. The physician's usual clinical practice for the management of LHON patients was followed which generally entailed clinic visits at 3 monthly intervals.

This EAP did not meet the criteria for a clinical trial under the scope of Directive 2001/20/EC and was not conducted in compliance with GCP standards applicable to clinical trials.

Study participants:

The main criteria for inclusion were a diagnosis of LHON with confirmed LHON mtDNA mutation type and onset of vision loss in the second eye less than 12 months prior to the date of the Baseline visit.

Patients were included in the EAP from Germany, United Kingdom, Australia, New Zealand, Poland, Sweden, Spain, Turkey, Switzerland and the United States of America.

At the time of the data cut for the initial report submitted with this Application (31 January 2014), 61 patients had been enrolled in the EAP safety population and had received at least one dose of Raxone. The efficacy population was a sub-population of the safety population who carried one of the 3 major LHON-causative mtDNA mutations for whom post-Baseline VA efficacy data was available (n=48).

During the course of the assessment, the Applicant provided an updated EAP report (clinical cut off on 20 March 2015) including 93 patients in the safety population and 69 patients in the efficacy population.

Treatment:

All patients received idebenone 150 mg film-coated tablets, usually at the recommended dose of 900 mg/day.

Primary Efficacy Endpoints: Proportion of patients with CRR in VA from nadir (as defined by Carelli et al., 2011).

Secondary Efficacy Endpoints:

- The proportion of patients with CRR by mutation
- The proportion of patients with CRR by gender, age at Baseline, smoking status, duration of disease at Baseline and VA at nadir
- Duration of Raxone treatment at CRR
- The treatment effect size in VA in patients with CRR

In addition to these analyses, the proportion of patients in whom VA did not deteriorate after Raxone treatment initiation was assessed as follows:

- In patients who can read at least the equivalent of 1 line on-chart VA at Baseline (i.e. logMAR ≤1.60), the proportion of patients with no clinically relevant worsening (CRW) in VA at their last assessment (either deteriorating from logMAR ≤1.6 to "off chart" VA or by the equivalent of 10 letters on chart) in either eye.
- The proportion of patients who had not reached the threshold for legal blindness (i.e. VA logMAR <1.0) at Baseline who remained below this threshold (i.e. VA remained logMAR <1.0) at their last assessment in either eye.

Results:

Demographics of the patients enrolled in the EAP were generally representative of the disease characteristics of LHON with respect to age at onset of symptoms (Onset), mtDNA mutation carried, gender distribution and smoking status and were similar across both populations. The average age at Baseline was 30.9 years (range 6.9 – 80.1) and 6 patients below the age of 14 were included. The distribution of the three major mtDNA LHON-causative mutations was 59% for the G11778A, 18% for the G3460A and 16.4% for the T14484C mtDNA mutations. The mean time since onset at Baseline was 10.6 months (range 0.9 – 133.7) for all enrolled patients but was shorter in the efficacy population (mean 7.2 months, range 0.9-21.5).

At the time of the initial report, of the 48 patients in the efficacy population, 44 and 23 had received Raxone treatment for at least 6 and 12 months, respectively. Overall, 24 out of 48 patients (50%) and 37 out of 96 eyes (38.5%) had presented with CRR from nadir by the respective last VA assessment. Of the 24 responders, a total of 13 (54.2%) had CRR in both eyes. Proportions of CRR by mtDNA mutation carried, were T14484C (88.9%), G3460A (70.0%) and G11778A (31.0%). Similar results were seen in the updated report, whereby CRR was observed in 34 out of 69 patients (49.3%) and 55 out of 138 eyes (39.9%).

In the updated report submitted during the course of the assessment (clinical cut off 20 March 2015), of the 69 patients in the efficacy population, 63 had received Raxone treatment for at least 6 months and 45 for 12 months. The maximum treatment period was 36 months (2 patients) and the mean treatment duration was 15.4 (range 2.8 – 36.2) months. Of the patients for whom 6 month (± 3 months, n=62) or 12 month (± 3 months, n=47) VA assessments were available, CRR had occurred in 19 (30.6%) patients and 30/124 (24.2%) of eyes at the 6 month assessment and in 17 (36.2%) patients and 28/94 (29.8%) of eyes at the 12 month assessment.

Age at Baseline, sex and smoking status did not appear to influence CRR.

The time from start of Raxone treatment to CRR was ≤6 months in 18 out of 24 patients (75%) and 20 out of 24 patients (83.3%) presented with CRR within 12 months of Baseline. The mean treatment time from Baseline to first CRR event was 6.6 months (range 2.5-19.9), whilst the mean overall treatment time in patients with CRR at last observation was 11.6 months.

With regard to the effect of time since onset at Baseline, of the 26 patients who had time since onset ≤6 months in their 1st eye at Baseline, 10 (38.5%) presented with CRR. Of the patients with time since onset of >6-12 (n=15) and >12-24 (n=7) months at Baseline, 60% and 71.4% presented with CRR respectively.

To further explore the impact of time to disease onset, on request by the CHMP, the Applicant carried out an analysis which showed that early treatment with idebenone ameliorated the degree of VA loss at nadir. As could be expected, the mean VA at Baseline for all eyes with disease onset of ≤6 month prior to treatment initiation was lower than that of >6 month eyes (logMAR 1.25, n=59 versus logMAR 1.49, n=37, respectively). However, the mean VA at nadir was also lower in ≤6 month eyes compared to >6 month eyes (logMAR 1.44 versus logMAR 1.51). Furthermore, in absolute terms, the outcome for >6 month eyes was not improved over the outcome for ≤6 month eyes (logMAR 1.21 versus logMAR 1.25). When considering only the proportions of eyes with CRR, VA at Baseline, Nadir and Outcome were 1.16, 1.30 and 0.68 versus 1.37, 1.39 and 0.85, respectively for ≤6 month (18 eyes) and >6 month eyes (19 eyes).

2.5.3.3. Natural History Case Record Survey (CRS)

The primary objective of the CRS (SNT-IR-006) was to gather further clinical data in order to establish the natural course of vision loss and recovery in patients with a genetically confirmed diagnosis of LHON.

To this end, historically documented VA data from existing medical records were collected from participating European Vision Institute Clinical Research Network (EVICR.net) member centres, as well as from LHON-treating centres in the EAP. A total of 11 centres provided CRS data with 10 located in Europe and 1 in the United States of America.

This CRS does not meet the criteria for a clinical trial under the scope of Directive 2001/20/EC and was not conducted in compliance with GCP standards applicable to clinical trials.

Diagnosis and Main Criteria for Inclusion: Participating clinical centres were asked to provide historical case record data from all LHON patients (with molecular diagnosis) on file without pre-selection.

Number of Case Records collected and analysed: 383

The population for the Primary Endpoint analysis included 106 patient records and 890 VA assessments made ≤2 years after onset of symptoms from patients with no recorded idebenone use, who carried one of G11778A, G3460A or T14484C mtDNA mutations and for whom the date of onset of symptoms was known (Natural History Population).

For the Secondary Endpoint analyses, 74 patient records were available, including 774 VA assessments from patients in the Natural History Population for whom data from at least one post-presentation VA assessment made ≥3-24 months post-presentation (Natural History Outcomes Population).

Within the analysed case records, idebenone use was reported by 188 patients. Application of the same criteria as for the definition of the Natural History Outcomes Population, identified 48 patients that were analysed alongside the natural history data.

Treatment: The CRS targeted patients not receiving idebenone treatment. Within the Idebenone-Treated Outcomes Population, the average dose used was 520 mg/day (median 405 mg/day; range 60-900 mg/day) and the mean duration of therapy was 1.5 years.

Primary endpoint: VA as a function of time since onset of symptoms.

Secondary endpoints:

- Proportion of patients with spontaneous clinically relevant recovery (sCRR) from VA nadir by disease history and mutation status
- Time to any sCRR from VA nadir
- The magnitude of any sCRR from VA nadir
- Proportion of patients with no clinically relevant deterioration in VA

Summary of Results:

Without Idebenone Treatment

Sixty-one per cent of eyes were already legally blind at presentation, of which 22% had already deteriorated to “off-chart” VA. At nadir 96% of eyes were legally blind and 75% had deteriorated to off-chart VA. By the time of the last available VA data point (mean 14.9 months after Onset; range 3.9–31.1 months), which was used as the outcome VA, 83% of the patients remained blind.

VA data from the Natural History Population reflected the very rapid loss of VA characteristic of LHON with over 50% of eyes deteriorating to logMAR ≥ 1.0 within 1 week of disease onset, increasing to over 70% within 3 months. By 12 months over 80% of patients’ eyes were legally blind. In the 142 observations available for 12 to 24 months of onset, 78% of eyes remained legally blind.

Overall, sCRR in VA from nadir was observed in at least one eye of 23 out of 74 patients (31.1%) and in 36 out of 148 eyes (24.4%). As 36 eyes from 23 patients experienced sCRR, 13 of these patients improved with both eyes. The proportions of patients with sCRR appeared similar in patients with time since onset at presentation of ≤6 months (31.8%, 20/63) and >6-12 months (33.3%, 3/9). Analysis of the proportions of patients with sCRR by mtDNA mutation carried showed that higher proportions of sCRR were observed in patients carrying the G3460A (50.0%, 6/12) and T14484C (42.9%, 3/7) compared to patients carrying the G11778A mutation (25.5%, 14/55). In the 23 patients presenting with sCRR, the mean time from disease onset to sCRR was 9.9 months (1.0 – 27.5 months). Analysis of the magnitude

of the best sCRR observed for either eye in patients with sCRR revealed a mean value of 39 letters, ranging from 5 to 90 letters. Additionally, only 20.9% of patients with on-chart vision (n=67) had no CRW of VA post-presentation in at least one eye and only 14.9% of the 47 patients who had VA logMAR <1.0 at presentation had maintained this status at the time of the latest VA outcome.

With Idebenone Treatment

The proportions of eyes with VA of logMAR <1.0, 1.0-1.68 or >1.68 were similar at Presentation between the idebenone-treated and untreated Outcome populations. CRR of VA from nadir was observed for 24 of 48 patients (50%) and 38 of 96 eyes (39.6%) had a CRR. In these patients, the mean time from onset to CRR was 16.2 months (range from 1.9 – 39.4 months. The mean magnitude of the best CRR (considering the best recovering eye in each patient), was 38 letters and ranged from 8 letters to 82 letters. Furthermore, 14 out of 39 patients with on-chart vision at presentation (35.9%) and 29 of 71 eyes (40.8%) in the Idebenone-Treated Outcomes Population had no CRW in the VA of at least one eye. Of the 26 patients who had VA logMAR <1.0 at Presentation, 7 (26.9%) still had VA logMAR <1.0 at Outcome. Compared to the untreated Outcome population, fewer idebenone-treated eyes had off-chart VA and higher proportions had on-chart VA or were not legally blind at Outcome.

2.5.3.4. Summary of relevant published literature

The Applicant provided an overview of the scientific literature reporting on the use of idebenone in the treatment of LHON. Three retrospective open-label cohort studies (Mashima 2000; Carelli 2011; Orssaud 2012) and 7 case reports (Mashima 1992; Carelli 1998a; Carelli 1998b; Carelli 2001; Barnils 2007; Jancic 2011; Peyman 2012) were summarised, collectively reporting on VA outcomes of 143 LHON patients treated with idebenone.

The majority (127 patients, 89%) of patients described in these studies were from Europe (Italy, France, Spain, Serbia). The duration of idebenone treatment ranged from 6 months up to 5 years, with 131 patients (92%) treated for at least 12 months. The idebenone doses used in these 10 studies ranged from 90 mg/day to 900 mg/day with a majority of patients receiving 270-675 mg/day.

Mashima (2000) and Carelli (2011) reported the proportion of patients with medically-relevant improvement of VA for patients with the G11778A mtDNA mutation (vast majority of patients living in Europe) and disease onset ≤ 1year before treatment as follows:

- Responders with VA recovery ≥ 0.3 (decimal acuity) in patients treated with idebenone was 26.4% (4 of 11 patients) compared to 10.0% (1 of 10 patients) in the untreated comparator group (Mashima 2000).
- Responders with VA improvement by 2 lines on a Snellen Chart or from “off-chart” to “on-chart” vision in patients treated with idebenone was 46.7% (14 of 30 patients) compared to 23.3% (10 of 43 patients) in the untreated comparator group (Carelli 2011).

2.5.4. Analysis performed across trials

In order to compare the results from the different data sources, a comparison of the outcomes for Raxone/idebenone-treated patients with placebo/untreated patients was presented for RHODOS, the EAP and the CRS. Table 12 provides a summary of the results for the proportions of patients with CRR, the proportions of patients without clinically relevant deterioration in VA and/or the proportions without deterioration in VA to logMAR ≥1.0 (legal blindness).

Table 12 – Selected Outcomes for RHODOS, the EAP and the CRS

Outcomes (patients)		RHODOS		EAP	CRS	
		Placebo	Raxone®	Raxone®	Untreated	Idebenone
CRR	(n/Total, %)	3/28 10.7%	18/53 34.0%	24/48 50.0%	23/74 31.1%	24/48 50.0%
No deterioration in VA	(n/Total, %)	n.d.	n.d.	24/38 63.2%	14/67 20.9%	14/39 35.9%
No deterioration in VA to ≥ 1.0 logMAR	(n/Total, %)	0/2 0.0%	6/6 100.0%	9/13 69.2%	7/47 14,9%	7/26 26.9%

n.d.: Not determined using the same definition

Across all studies, 66/149 (44.3%) Raxone/idebenone-treated patients presented with CRR compared to 26/102 (25.5%) of placebo/untreated patients with sCRR using the same stringent definition of CRR.

To further facilitate comparison of the findings in the EAP and CRS, a graphical comparison of the VA data at different time points was provided (Figure 4).

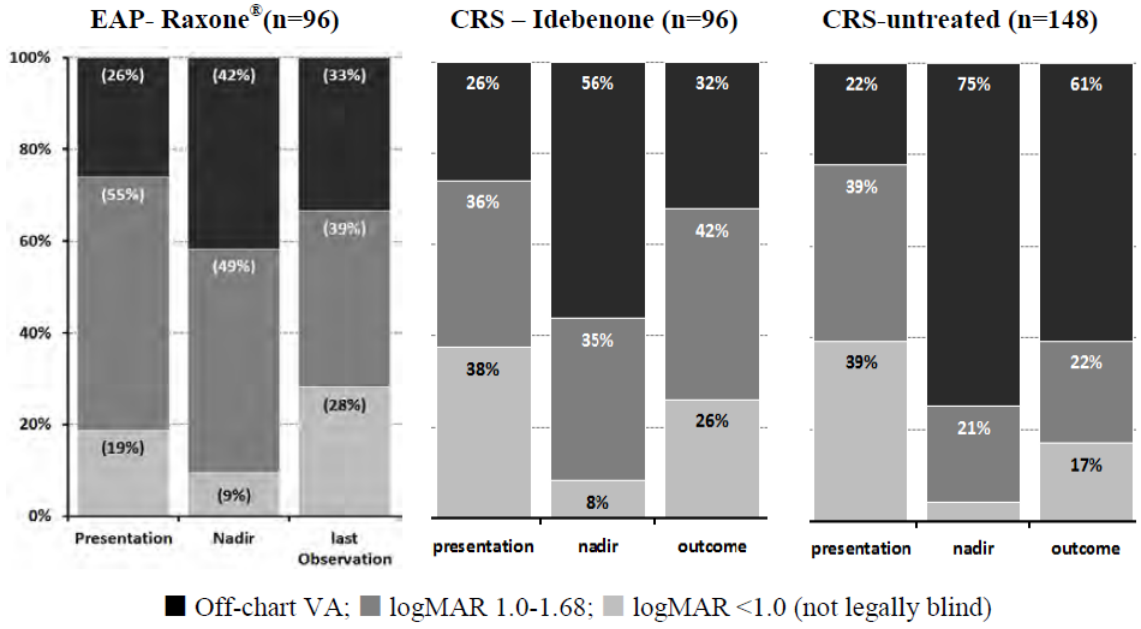


Figure 4 - Comparison of Analyses by VA Category for Eyes at Presentation, Nadir and Outcome for Raxone / idebenone-treated and untreated Patients

The data show a similar outcome for patients treated with idebenone across data sets (EAP and CRS), and in both cases a larger number of patients with logMAR<1.0 and a smaller number of legally blind and patients with off-chart vision compared to idebenone-naïve patients.

Due to the complex heterogeneity of the Natural History Population studied, i.e., a population of different distribution of patients at different stages of LHON presentation of symptoms (the nadir is at different time points) as well as the limitation of the number of VA observations, nadir might not have been established in some patients and this could affect the outcomes reported. Nevertheless, the CHMP was of the opinion that the outcome of CRS and EAP could potentially provide independent confirming evidence of efficacy of Raxone if data would be adequately analysed and presented. To facilitate the bridging across data sets, additional analyses and graphical presentations were requested to allow comparison of CRS data with the RHODOS placebo outcome and of EAP data with the RHODOS idebenone outcome. In these analyses, VA improvement was to be measured based on change to baseline/presentation instead of

nadir, as a post nadir recovery concept for the purpose to compare recovery outcome data of different study data sets (i.e. RHODOS, EAP and CRS), where important characteristics such as time since onset showed marked differences, was considered unsuitable.

In response to the request, the Applicant provided additional analyses of responder outcomes (CRR and CRW) both on a "per eye" or on a "per patient" level and by VA status (off-chart or on-chart) and for short-term observations (6 months) and long-term data (36 months). The results are shown in Table 13, Figure 5 and Figure 6.

CRR was defined as follows:

- All eyes/patients (requests 6, 7, 10a and 17-19): For off-chart (HM or worse) at baseline, any improvement to the next better off-chart category (intra-off categories) or improvement to on-chart is considered a response; for off-chart (CF) at baseline response is defined as being able to read at least 5 letters on-chart at week 24; for on-chart at baseline improvement is defined as VA improved by ≥ logMAR 0.2 at week 24 (at patient level: CRR in at least one eye).
- All patients (request 14, 15 and 16): CRR in at least one eye - Definition as per post-hoc analyses in RHODOS.
- Off-chart eyes/patients with both eyes off-chart at baseline (requests 1-3 and 11-13: Definition as per post-hoc analyses in RHODOS (at patient level: CRR in at least one eye).
- On-chart eyes at baseline (requests 4 and 5): Definition as per post-hoc analyses in RHODOS.

CRW was defined as follows:

- All eyes/patients (8, 9, 10b and 20-22): For off-chart at baseline, any worsening to the next worse off-chart category is considered a worsening; for on-chart > 1.6 logMAR at baseline any worsening to at least HM off-chart is considered a worsening; for on-chart ≤ 1.6 logMAR at baseline worsening is defined as VA worsened by ≥ logMAR 0.2, or by worsening to off-chart at week 24 (at patient level: CRW in both eyes)

Graphical presentations of VA changes over time, taking into account time to onset and time to baseline/presentation, were also provided.

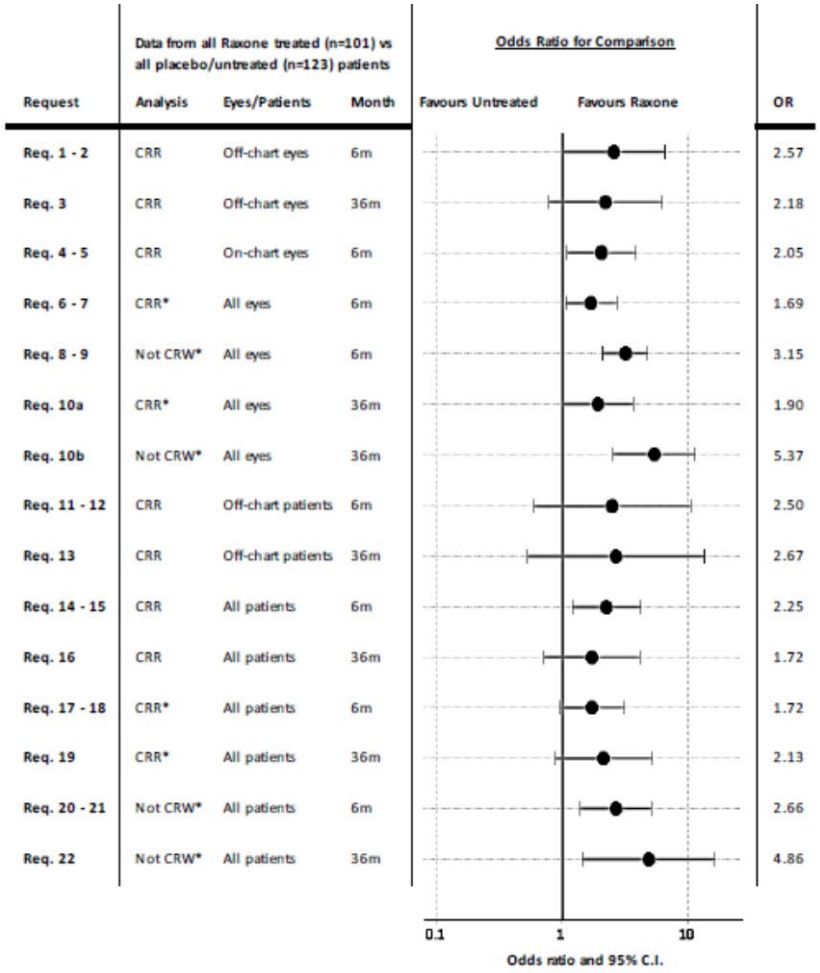
Table 13 – Results of additional CRR and CRW Analyses by Data Set (RHODOS Idebenone Group = RHO-IDE; RHODOS Placebo Group = RHO-PLA, EAP and CRS)

Request	Analysis	Eyes/Patients	Month	Group	Total (N)	Resp. (N)	Resp. (%)
Req. 1	CRR	Off-chart eyes	6m	RHO-IDE	61	12	19.7%
Req. 1	CRR	Off-chart eyes	6m	EAP	25	6	24.0%
Req. 2	CRR	Off-chart eyes	6m	RHO-PLA	29	0	0.0%
Req. 2	CRR	Off-chart eyes	6m	CRS	46	7	15.2%
Req. 3	CRR	Off-chart eyes	36m	RHO-PLA	19	2	10.5%
Req. 3	CRR	Off-chart eyes	36m	CRS	10	5	50.0%
Req. 4	CRR	On-chart eyes	6m	RHO-IDE	45	9	20.0%
Req. 4	CRR	On-chart eyes	6m	EAP	71	17	23.9%
Req. 5	CRR	On-chart eyes	6m	RHO-PLA	29	4	13.8%
Req. 5	CRR	On-chart eyes	6m	CRS	141	17	12.1%
Req. 6	CRR*	All eyes	6m	RHO-IDE	106	25	23.6%
Req. 6	CRR*	All eyes	6m	EAP	96	24	25.0%
Req. 7	CRR*	All eyes	6m	RHO-PLA	58	8	13.8%
Req. 7	CRR*	All eyes	6m	CRS	187	31	16.6%
Req. 8	Not CRW*	All eyes	6m	RHO-IDE	106	94	88.7%
Req. 8	Not CRW*	All eyes	6m	EAP	96	62	64.6%
Req. 9	Not CRW*	All eyes	6m	RHO-PLA	58	44	75.9%
Req. 9	Not CRW*	All eyes	6m	CRS	187	83	44.4%
Req. 10a	CRR*	All eyes	36m	RHO-PLA	38	12	31.6%
Req. 10a	CRR*	All eyes	36m	CRS	45	12	26.7%
Req. 10b	Not CRW*	All eyes	36m	RHO-PLA	38	23	60.5%
Req. 10b	Not CRW*	All eyes	36m	CRS	45	19	42.2%
Req. 11	CRR	Off-chart patients	6m	RHO-IDE	25	7	28.0%
Req. 11	CRR	Off-chart patients	6m	EAP	8	2	25.0%
Req. 12	CRR	Off-chart patients	6m	RHO-PLA	13	0	0.0%
Req. 12	CRR	Off-chart patients	6m	CRS	10	3	30.0%
Req. 13	CRR	Off-chart patients	36m	RHO-PLA	8	2	25.0%
Req. 13	CRR	Off-chart patients	36m	CRS	3	1	33.3%
Req. 14	CRR	All patients	6m	RHO-IDE	53	16	30.2%
Req. 14	CRR	All patients	6m	EAP	48	16	33.3%
Req. 15	CRR	All patients	6m	RHO-PLA	29	3	10.3%
Req. 15	CRR	All patients	6m	CRS	94	18	19.1%
Req. 16	CRR	All patients	36m	RHO-PLA	19	8	42.1%
Req. 16	CRR	All patients	36m	CRS	23	9	39.1%
Req. 17	CRR*	All patients	6m	RHO-IDE	53	17	32.1%
Req. 17	CRR*	All patients	6m	EAP	48	17	35.4%
Req. 18	CRR*	All patients	6m	RHO-PLA	29	6	20.7%
Req. 18	CRR*	All patients	6m	CRS	94	22	23.4%
Req. 19	CRR*	All patients	36m	RHO-PLA	19	9	47.4%
Req. 19	CRR*	All patients	36m	CRS	23	9	39.1%
Req. 20	Not CRW*	All patients	6m	RHO-IDE	53	50	94.3%
Req. 20	Not CRW*	All patients	6m	EAP	48	35	72.9%
Req. 21	Not CRW*	All patients	6m	RHO-PLA	29	24	82.8%
Req. 21	Not CRW*	All patients	6m	CRS	94	58	61.7%
Req. 22	Not CRW*	All patients	36m	RHO-PLA	19	15	78.9%
Req. 22	Not CRW*	All patients	36m	CRS	23	12	52.2%

CRR: clinically relevant recovery; CRW: clinically relevant worsening

CRR and CRW* include intra-off categories as requested*

Placebo/untreated patients shaded in grey



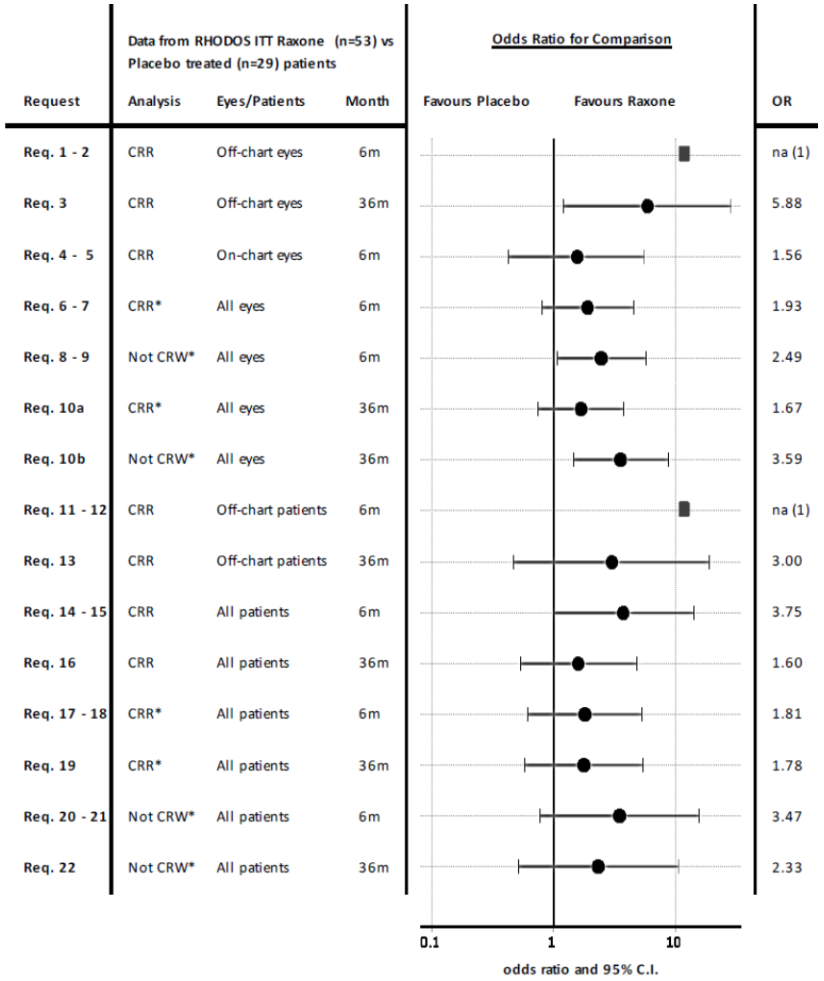
Req.: requested analyses in same order as defined in the Annex to MO18

CRR: clinically relevant recovery; CRW: clinically relevant worsening; OR:odds ratio

CRR and CRW* include intra-off categories as requested*

Month: Time since Baseline/Presentation

Figure 5 – Odds Ratios for the Comparison of All Raxone Treated Patients (RHODOS Idebenone Group and EAP) versus All Untreated Patients [RHODOS Placebo Group (ITT) and CRS]



Req. : requested analyses in same order as defined in the Annex to MO18

CRR: clinically relevant recovery; CRW: clinically relevant worsening; OR:odds ratio

CRR and CRW* include intra-off categories as requested*

Month: Time since Baseline/Presentation

(1) No responders in the Placebo group; Odds ratio cannot be estimated but set > 10 to reflect favourable outcome for Raxone

Figure 6 - Odds Ratios for the Comparison of RHODOS Idebenone Group versus Placebo Group (ITT)

Tabular presentations in response to analysis requests 6 + 7 (all eyes) and 17 + 18 (all patients) show the results for CRR (including intra-off-chart-improvements) in VA after 24 weeks compared to baseline/presentation for all idebenone treated patients (RHODOS idebenone treatment arm and the EAP) versus placebo/natural history data (RHODOS placebo treatment arm data and CRS). Results for analyses 6+7 show a higher proportion of eyes with CRR in the idebenone group [RHODOS idebenone: 23.6% (25/106) and EAP: 25.0% (24/96)] than in untreated eyes [RHODOS placebo: 13.8% (8/58) and CRS: 16.6% (31/187)]. The estimated unadjusted odds ratio (OR) based on data-pooling for treated and untreated conditions over trials was OR=1.69 (95% CI: [1.06; 2.71]). Corresponding analyses (request 17 + 18) on the per-patients level shows similar results [RHODOS idebenone: 32.1% (17/53) and EAP: 35.4% (17/48) versus RHODOS placebo: 20.7% (6/29) and CRS: 23.4% (22/94); OR=1.72, 95% CI: (0.96; 3.11)]. Similarly, CRR regardless of intra-off-chart-improvements (request 14 and 15) was consistently higher for idebenone treated patients [RHODOS idebenone: 30.2% (16/53) and EAP: 33.3% (16/48)] than for untreated patients [RHODOS placebo: 10.3% (3/29) and CRS 19.1% (18/94); OR=2.25, 95% CI: (1.20; 4.23)].

Results of request 11 and 12 (CRR in at least one eye in patients, who were off-chart at baseline in both eyes) revealed a higher estimated proportion of CRR for untreated off-chart patients included in the CRS [RHODOS Placebo: 0.0% (0/13) and CRS 30.0% (3/10)] than for idebenone treated patients [RHODOS idebenone: 28.0% (7/25) and EAP 25.0% (2/8)]. However, the sub-set of patients was rather small and estimates have low precision.

For the endpoint 'no CRW' (request 20 + 21; CRW in both eyes including intra off-chart categories), response rates in the untreated and treated conditions were found to be heterogenic and in rather high ranges (RHODOS idebenone: 94.3% (50/53) and EAP 72.9% (35/48) versus RHODOS placebo: 82.8% (24/29) and CRS 61.7% (5/91)].

Data from untreated patients after 36 months showed a higher proportion of patients/eyes with CRR compared to treated patients after 6 months. Point estimates for CRR (including intra-off-chart-improvements) of all eyes after 6 months treatment was 23.6% and 25.0% for RHODOS idebenone group and EAP, respectively, whereas corresponding rates after 36 months without treatment were 31.6% (12/38) and 26.7% (12/45) for RHODOS placebo group and CRS, respectively (request 6 + 10a). Corresponding analyses on the per-patient revealed the following estimates after 6 months treatment: 32.1% for RHODOS idebeone and 35.4% for EAP, and after 36 months recovery rates observed without treatment were 47.4% (9/19) and 39.1% (9/23) for RHODOS placebo and CRS, respectively (Requests 17 + 19). CRR (without intra-off-chart-improvements) of patients after 6 months treatment was 30.2% and 33.3% for RHODOS idebenone and EAP, respectively, and after 36 months without treatment 42.1% (8/19) and 39.1% (9/23) for RHODOS placebo and CRS, respectively (requests 14 + 16).

2.5.5. Discussion on clinical efficacy

The main evidence for efficacy of Raxone in the treatment of patients with LHON's disease was derived from the pivotal phase II trial RHODOS as complemented by data from a single open label follow-up visit (RHODOS-OFU). Further supportive data were available form an Expanded Access Programme (EAP), a Natural History Case Record Survey (CRS) and the scientific literature. The latter data had not been available in a previous Application made in 2011, that was withdrawn in 2013.

No dose-response studies were conducted. The choice of the dose (2x150mg t.i.d.; 900mg/day) investigated in RHODOS and proposed for commercial use was based on the available information prior to the start of the RHODOS trial, including extrapolation of non-clinical data for the effective dose preventing retinal ganglion cell (RGC) death in animal models. Based on these data, the selected dose was

considered to be in a range of a plausible pharmacodynamic effect in humans. The CHMP furthermore acknowledged that due to the rarity of the disease, dose-ranging studies would be difficult to conduct.

Design and conduct of clinical studies

The pivotal RHODOS study was a double-blind, randomised, placebo-controlled, parallel group trial. The design and conduct of the study were generally considered acceptable by the CHMP. While the size of the study was limited with 85 patients, as was to be expected for a trial in a rare disease, the study population was considered largely representative of LHON patients, whereby LHON typically affects young adult males. Baseline characteristics of the two treatment groups were balanced including time since disease onset and mutation type. However, inclusion of patients with onset of vision loss within 5 years of enrolment into the RHODOS trial resulted in a heterogeneous population, with patients being at different stages in the disease progression and having different degrees of visual impairment.

With regards to the EAP, which was primarily established to grant access to Raxone to individual "named" LHON patients at the request and under the personal care of a registered physician, it could not be excluded with certainty that due to the open-label, uncontrolled nature of the data collection, bias had been introduced affecting the outcome of the study. Limitations also applied to the natural history data in the CRS due to methodological constraints resulting from the retrospective analysis of patient records and differences in data (VA measurements) collection. For these reasons, data from the EAP and CRS were only considered supportive.

The youngest patient recruited in RHODOS was 14 years at the time of enrolment. Limited data were available from the EAP and CRS for children and adolescents below the age of 14 years. The CHMP was of the opinion that the available data in their entirety justified consideration of adolescents in general for the indication, rather than a cut-off age of 14 years as initially proposed by the Applicant. This was also in line with the demographics of LHON disease, whereby disease onset has also been observed in younger children.

Patients in RHODOS were treated for a duration of 24 weeks and long-term follow-up data from RHODOS-OFU only provided information from a single visit about 2.5 years later for patients who previously participated in RHODOS, but did not receive any treatment thereafter. Additional, supportive long-term efficacy data were available from the EAP including 45 patients treated with idebenone for a least 12 months with a mean treatment duration of 15.4 (range 2.8 – 36.2) months.

The primary efficacy analysis in RHODOS was based on the ITT population. The Applicant also provided re-analyses based on a modified ITT (mITT) population, excluding one patient in the placebo group who spontaneously experienced a profound gain in VA commencing already before study start and who was therefore considered a "natural history confounder". However, the exclusion of this patient, who initially fulfilled the inclusion criteria, was considered by the CHMP to be contradictory to the ITT principle and questionable from a methodological point of view. The effect of inclusion/exclusion of this patients on the study results was well known and has been discussed by the CHMP in a previous Application. Exclusion of the patient from the analyses rendered the results of the key secondary endpoint statistically significant in favour of idebenone but not for the primary endpoint. This powerful effect of exclusion of a single patient had raised concerns within the CHMP about the extent of the impact of spontaneous regression as a possible confounding factor giving the small sample size in RHODOS. Consequently, the robustness of the RHODOS results were questioned. The position of the CHMP remained unchanged on this point. For the present Application, the efficacy assessment therefore focused on the added evidence obtained from the additional data (EAP and CRS) and analyses presented.

The efficacy assessment was mainly based on changes in visual acuity (VA) including several responder analyses, some of which were conducted post-hoc. Supportive non-VA endpoints included colour contrast

vision and quality of life. Both patient-based and eye-based analyses were conducted, which was considered adequate by the CHMP. Analyses by eyes allowed for control of time to disease onset, as onset of vision loss may significantly differ between the two eyes of a LHON patients. At the same time, analyses at patient level account for the dependency/correlation between the eyes of individual patients.

Amongst the additional post-hoc analyses, the CHMP considered the responder analysis of clinically relevant recovery (CRR) as defined by Carelli et al. (2011) to be a valuable marker for assessing treatment benefit, notwithstanding the usual limitations of the interpretability of post-hoc results. The CHMP furthermore acknowledged the concept of nadir, i.e. replacing baseline measurements by the worst VA at any time post-Baseline, as such analyses take into account that less severely affected patient with more recent disease onset might still not have reached nadir at the time of enrolment and only reach nadir in the course of the study. In comparison, for more severely or further progressed patients, nadir might have been established already at study baseline. Nevertheless, difficulties in the comparative data analyses arose from the lack of continuous VA measurements as discussed below.

Efficacy data and additional analyses

The primary endpoint in RHODOS (best recovery of logMAR VA in either right or left eye at 24 weeks of treatment) did not reach statistical significance with an estimated mean difference in best recovery of VA between the idebenone and placebo arm of logMAR -0.06, equivalent to 3 letters on a vision chart (p=0.291). The numerical difference in favour of idebenone increased to 5 letters when analyses were conducted on the mITT population. With regards to the key secondary endpoint, change in best VA, patients in the placebo group worsened by 4 letters (mean change logMAR 0.085), while patients on idebenone showed a slight improvement by 1 letter (mean change logMAR 0.035). As could be expected, the difference increased for the mITT population due to a larger loss of vision in the placebo group (difference in log MAR -0.160; 8 letters). The between-group difference was only statistically significant for the mITT population.

Other pre-defined secondary VA endpoints showed broadly similar results numerically in favour of idebenone. Patients receiving idebenone also had improved outcomes compared to placebo by the end of the study in colour contrast sensitivity and measurements of the retinal nerve fibre layer suggested a protective effect of idebenone in patients with disease onset of 6 months or less, albeit the number of patients for the majority of these analyses was small.

With regards to health related quality of life (HRQoL), self-reported energy levels and clinical global impression of change (CGIC), there was no significant difference between study arms. Moreover, in RHODOS-OFU, for the entire period between RHODOS Baseline to follow-up visit, there was a small worsening of the HRQoL score in the idebenone group (-1.7%) compared to a small improvement in the placebo group (2.4 %; p=0.205). While this finding might be explained by a lack of sensitivity of the HRQoL questionnaire used, which was originally developed for patient who underwent cataract surgery, it remained unclear if a possible treatment induced improvement in vision translated into benefits for the patient's daily activities.

Amongst the post-hoc responders analyses, the results for the proportion of patients/eyes with off-chart VA at Baseline who were able to read at least one full line on-chart at Week 24 were considered of clinical relevance by the CHMP as such a recovery was considered an important categorical change. In the sub-group of patients with off-chart vision in both eyes, 28% (7/25) of the Raxone-treated patients were able to read at least 5 letters on-chart at Week 24, but none of the 13 placebo treated patients (p=0.072). Similar results were obtained for the analysis per eyes. This analysis did however not adequately account for time since onset.

Supportive evidence for a treatment effect of idebenone was furthermore available from the post hoc analysis of the proportion of patients with CRR of VA from Baseline. A higher proportion of patients in the Raxone group (16/53 patients, 30.2%) than in the placebo group (ITT: 3/29 patients, 10.3%, mITT: 2/28 patients, 7.1%) had CRR in at least one eye. The between-group difference was statistically significant when analyses were conducted on the mITT population (p=0.0234). Similar results were obtained when CRR was determined compared to patients' nadir.

Additional supportive data from the EAP showed that 50% (24/48) of patients and 38.5% (37/96) of all eyes had CRR from nadir (in at least one eye for the analysis at patient level) at the last available assessment. In comparison, data from the natural history CRS showed that only 31.1% (23/74) of untreated patients experienced spontaneous CRR from nadir.

Comparison across data sets including RHODOS study data was however hampered by the heterogeneity of patients and lack of continuous VA measurements over time, which affected determination of nadir. To enable bridging of data, additional responder analyses were requested by the CHMP abandoning the concept of nadir and differentiating between off-chart and on-chart vision as well as study duration. Based on these analyses, across data sets and when pooling data, generally a larger proportion of patients/eyes treated with idebenone with CRR were observed compared to placebo. Some of the analyses were based on small subgroup sizes and calculation of odds ratios did not account for confounding factors such as time to disease onset. Visual control of the distribution of time since onset however did not give particular rise of concern for confounding. Thus, while still not demonstrating a clear, distinct treatment effect of idebenone, the requested analyses showed a consistent pattern of beneficial trends in favour of idebenone, although in the interpretation of these results it has to be kept in mind that response rates following different response definitions are highly correlated by nature.

Another observation when comparing data across data sets was the consistently lower rates of CRR in RHODOS compared to the EAP and the CRS. In fact, the proportion of patients with CRR in the natural history outcome population of the CRS (31.1%, 23/74 patients) was similar to the results for the idebenone treatment group in RHODOS (34.0%, 18/53 patients). The Applicant argued that the lower rates of CRR in RHODOS were due to the shorter duration of treatment. Indeed, when comparing data across data sets from untreated patients after 36 months, there was a higher proportion of patients/eyes with CRR compared to treated patients after 6 months.

These results created uncertainties of the long-term benefit of idebenone-treatment despite the observed trend for an improvement in vision in RHODOS-OFU over time. In RHODOS-OFU, after a mean time of 2.5 years from Week 24 in RHODOS, similar improvements in VA were observed for the idebenone and the placebo group. The in-between group difference was maintained, suggesting that the benefit obtained with idebenone after 6 months treatment persisted even after withdrawal of treatment. The overall tendency of improvement in vision in patients appeared to be mainly driven by patients with shorter disease history. During early stages of the disease, LHON patients can learn to cope with the central scotoma by using peripheral vision instead of foveal vision for object recognition. However, due to the lack of intermediate assessments in RHODOS-OFU, the detailed time courses for changes in both treatment arms from the end of RHODOS to the OFU visit were not known.

Limited support for an additional benefit of treatment beyond 6 months was available from the EAP. Of the patients in the EAP for whom 6 (± 3 months, n=62) or 12 month (± 3 months n=47) VA assessments were available, CRR had occurred in 19 (30.6%) patients and 30/124 (24.2%) of eyes at the 6 month assessment and in 17 (36.2%) patients and 28/94 (29.8%) of eyes at the 12 month assessment. Nevertheless, based on the available data at the time of this report, no firm conclusions could be drawn and no recommendation on treatment duration could be made. To address this issue, the CHMP was of the opinion that further long-term efficacy data should be collected post marketing.

Finally, several subgroup analyses have been conducted on the RHODOS data including analyses by disease onset, mutation type, age and smoking status. Despite the limitations of such analyses due to the small group sizes, compared to the overall population generally larger effect sizes in favour of idebenone were observed in patients with G11778A and G3460A mutations, patients with disease onset less than a year as well as non-smokers and younger patients. Univariate analysis for possible prognostic factors for treatment response showed that the T14484C mutation was associated with a higher proportion of responding patients compared to non-responders, which was expected due to the more benign course of the disease in patients with this mutation. However, based on the available data, it could not be excluded that patients with this mutation might benefit from idebenone treatment as well. This was in line with a recommendation from experts consulted in a previous Application. No other prognostic factors were identified as influential for the responder rate.

With regards to the impact of time since disease onset, in contrast to the subgroup analyses in RHODOS, data from the EAP showed an increase in the CRR rate from nadir apparently associated with late treatment. Additional analyses performed by the Applicant, however, suggested that early treatment with idebenone ameliorated the degree of VA loss at nadir, thus explaining the reduced effect size for CRR responder rates in patients with more recent onset of vision loss. The outcome for early versus late-treated eyes was similar. A plausible explanation for the mechanism of action underlying the clinical observations could be that rapid vision loss at disease onset is caused by RGC inactivation but, as long as the RGCs remain viable, recovery of vision is possible through restoration of mitochondrial function. The natural history of LHON suggests that recovery of vision is possible even after years of vision loss, supporting the notion that inactive RGCs can remain viable for extended periods of time. Therefore, the CHMP considered that the indication should not be constrained by time to disease onset.

Evidence from the published literature for efficacy of idebenone in the treatment of LHON was rather limited and affected by publication or selection bias. Overall, the submitted literature seemed to indicate a favourable effect of idebenone. However no firm conclusions could be drawn from these data alone.

Additional efficacy data needed in the context of a marketing authorisation under exceptional circumstances

Taking into account the totality of the available data, the CHMP was of the view that the data set on the clinical efficacy of Raxone under normal conditions of use could not be considered comprehensive, nor was it considered feasible to generate a comprehensive data set mainly due to the rarity of LHON's disease. Furthermore, at the time of this report, idebenone was already used to treat LHON patients in clinical practice, whereby neither physicians nor patients would be prepared to participate in a placebo-controlled trial, thus preventing the generation of new controlled data to confirm the outcomes observed in RHODOS, the EAP and the CRS.

Following an oral explanation by the Applicant, the CHMP agreed that it was not feasible to produce a comprehensive data set under normal conditions of use of Raxone. The CHMP was furthermore of the view that a marketing authorisation under exceptional circumstances should be granted subject to a number of specific obligations in line with a program of studies proposed by the Applicant. Within this program, additional efficacy data should be generated through an open label interventional study in LHON patients treated with idebenone with an external natural history control based on an extended case record survey. This study should also provide data on long-term efficacy suitable to make recommendations on the duration of idebenone treatment. Furthermore, follow-up data from the ongoing EAP should be provided. In addition, a drug exposure registry should be conducted (see section 2.6.1.). While this study is mainly intended for the generation of further safety data, data on long-term effectiveness and lack or loss of therapeutic response should also be generated. The specific obligations will be reviewed annually and continuation of the authorisation shall be linked to these annual re-assessments.

2.5.6. Conclusions on the clinical efficacy

For the evaluation of the efficacy of Raxone in the treatment of LHON, the CHMP considered the totality of the available data, including in addition to the pivotal RHODOS trial, data from the EAP, the natural history CRS and the scientific literature. Notably, the CRS represented a rather unique dataset enabling a better understanding of the natural course of LHON's disease. Overall, the CHMP was of the view that data from the EAP and the CRS provided independent supportive evidence in favour of a treatment effect of idebenone, despite the limitations of some of the post-hoc analyses conducted across data sets, thus addressing concerns about the robustness of the RHODOS data.

In conclusion, the CHMP was of the view that there was a consistent trend of a beneficial effect of idebenone throughout the analyses conducted and across all available datasets which, while still lacking statistically significance for the majority of endpoints and when the usual methodological rigour was applied, was considered sufficiently convincing to support the Application for Raxone in the treatment of visual impairment in adolescent and adult patients with LHON.

However, the CHMP considered that the available data set on the clinical efficacy was not comprehensive and therefore considered the following measures necessary to generate additional efficacy data in the context of a marketing authorisation under exceptional circumstances:

- The MAH should conduct and submit the results of an external natural history controlled, open-label intervention study to assess the efficacy and safety of Raxone in the treatment of LHON patients, including long-term treatment.
- The MAH should maintain and extend the Historical Case Record Survey of Visual Acuity Data from Patients with LHON to serve as the external control to the open label study.
- The MAH should follow up patients in the existing Expanded Access Programme and submit the final results.

2.6. Clinical safety

Safety data in support of this Application were available from the pivotal double-blind, randomised, placebo-controlled study in LHON patients (RHODOS, SNT-II-003) as well the single open-label follow-up visit (RHODOS-OFU, SNT-II-003 OFU). Additional supportive data were presented from the clinical development program for Friedreich's ataxia (FRDA), as well as several Phase I studies in healthy volunteers. In summary, the following clinical data were reviewed:

- Pivotal Phase II, double-blind, randomised, placebo-controlled study in LHON patients RHODOS and observational follow-up study in patients completing RHODOS (RHODOS-OFU).
- Three double-blind, randomised, placebo-controlled, multi-centre studies in FRDA: NICOSIA (SNT-II-002), IONIA (SNT-III-002) and MICONOS (SNT-III-001). In addition, data from open-label, long-term extension trial of MICONOS and IONIA were provided.
- Four Phase I studies in healthy volunteers: SNT-I-001, SNT-I-002, SNT-I-003, and SNT-I-004.
- Data from post-marketing surveillance and EAP (see section 'post-marketing experience').

The Phase I studies were considered to provide limited safety data as they were conducted in small numbers of healthy volunteers, with a short duration of treatment (maximum 2 weeks dosing). For this reason and since there was no major safety finding in these studies, the data are not further discussed in this section.

Safety was assessed by evaluation of treatment-emergent adverse events (TEAEs), i.e., events which started or worsened during the study treatment. Relationship to study drug was defined as probable, possible, unlikely or unrelated. For analysis purposes, the relationship was converted to 'related' (probable, possible or unlikely) or 'unrelated' (unrelated). All adverse events (AEs) were considered related to treatment if the causal relationship was unknown or missing. Additionally, physical examination data, vital signs, electrocardiogram (ECG) and haematological and biochemical laboratory parameters in blood and urine samples were assessed.

Patient exposure

Overall, safety data were available for 311 subjects treated with idebenone and 124 treated with placebo. Of the idebenone treated subjects, 242 received idebenone at doses ≥900 mg/day. The safety population comprised both male and female subjects aged between 8 and 70 years, mostly of Caucasian/white race.

LHON patients

The Safety Population of Raxone included 85 patients, 55 treated with idebenone 900mg/day and 30 treated with placebo. Of the 55 patients enrolled in the idebenone arm, 52 subjects were exposed for 24 weeks (mean exposure time of 192 days). Three (3) and 4 patients discontinued in the active and the placebo treatment arms, respectively, including one patient in each arm who withdrew due to an adverse event. Patient demographics and baseline characteristics are summarised in Table 2 and Table 3 in section 2.5.2.

In RHODOS-OFU, patients were off-treatment, but 5 patients reported use of idebenone between Week 24 of RHODOS and the RHODOS-OFU visit.

FRDA patients

In the FRDA trials, patients were dosed based on their body weight (two different doses based on ≤ or > 45kg). A total of 256 FRDA patients received idebenone for up to 12 months, including 69 patients receiving 180/360 mg/day, 92 patients receiving 450/900 mg/day and 95 patients having had 1350/2250 mg/day. A total of 94 subjects received placebo. Overall, 332 subjects completed the respective treatment periods, including 243 who had received idebenone and 89 who had received placebo.

One hundred sixty (160) subjects with FRDA were exposed to idebenone for 12 months. Furthermore, a total of 68 subjects completed the IONIA study and entered the open-label, 12 months, single group extension study receiving 1350/2250 mg idebenone/day. The majority of subjects (86.8%) completed the extension study and the mean exposure was 338.5 days. In addition, 200 subjects completed the MICONOS study and entered the single group extension study, which ran for 24 months. Doses of 1350/2250 mg/day were used and 139 subjects (69.5% of enrolled patients) completed the study with a mean exposure over all previous treatment groups in the main study of 629.6 days.

Adverse events

LHON's disease

In the RHODOS study, the majority of subjects had at least one AE (89% for idebenone and 87% for placebo). The most common AEs (those with an occurrence of >5% in either group, regardless of causality) are collated in Table 14. Overall, the incidence of all AEs and treatment related AEs were low and similar or lower on idebenone compared with placebo.

The AEs reported by ≥10.0% of subjects on idebenone at the MedDRA preferred term (PT) level were: nasopharyngitis (25.5% of subjects affected), headache (23.6%), and influenza, blood triglycerides increased and cough (10.9% each). Headache, nasopharyngitis and cough were more frequent in the

idebenone group than the placebo group. In addition, dizziness was reported at a higher incidence in subjects receiving idebenone (5.5%) compared to subjects receiving placebo (0%).

Left ventricular hypertrophy (LVH) was reported for four subjects (7.3%) on idebenone but was not reported in the placebo group. Likewise, dizziness was reported for three subjects (5.5%) on idebenone but was not experienced by any subject in the placebo group. None of these AEs were of severe intensity and, with the exception of one episode of LVH, none were considered by the investigator to be related to idebenone treatment. The four cases of LVH were all reported by the same investigational site on the basis of the ECG readings only and the diagnosis was not supported by clinical or ultrasound evidence.

The majority of AEs were mild or moderate in intensity and only two subjects receiving idebenone experienced severe AEs. One patient had a severe headache considered unrelated to treatment, and the other had abnormal liver function test results that were considered possibly related to treatment and led to discontinuation.

Five subjects (four treated with idebenone and one treated with placebo) experienced treatment-related AEs. Blood triglycerides increased was reported for one subject in each treatment group, whereby the patient in the placebo arm also reported the treatment-related AE alanine aminotransferase increased. Furthermore, LVH, Wolff-Parkinson-White syndrome, and liver function tests abnormal were each reported for one subject (1.8%) in the idebenone group.

Table 14 – Common AEs (Reported by ≥5% of Subjects) in the RHODOS Study

N (%) subjects	Raxone® 900 mg/day (N=55)	Placebo (N=30)	All Subjects (N=85)
Cardiac disorders			
Left ventricular hypertrophy	4 (7.3)	0	4 (4.7)
Gastrointestinal disorders			
Abdominal pain upper	3 (5.5)	3 (10.0)	6 (7.1)
Constipation	2 (3.6)	3 (10.0)	5 (5.9)
Diarrhoea	5 (9.1)	3 (10.0)	8 (9.4)
Flatulence	0	2 (6.7)	2 (2.4)
Vomiting	4 (7.3)	2 (6.7)	6 (7.1)
Infections and infestations			
Gastroenteritis	1 (1.8)	2 (6.7)	3 (3.5)
Influenza	6 (10.9)	3 (10.0)	9 (10.6)
Nasopharyngitis	14 (25.5)	5 (16.7)	19 (22.4)
Sinusitis	1 (1.8)	2 (6.7)	3 (3.5)
Investigations			
Alanine aminotransferase increased	1 (1.8)	3 (10.0)	4 (4.7)
Blood cholesterol increased	0	2 (6.7)	2 (2.4)
Blood creatine phosphokinase increased	1 (1.8)	2 (6.7)	3 (3.5)
Blood triglycerides increased	6 (10.9)	3 (10.0)	9 (10.6)
Gamma-glutamyltransferase increased	0	5 (16.7)	5 (5.9)
Musculoskeletal and connective tissue disorders			
Arthralgia	0	2 (6.7)	2 (2.4)
Back pain	4 (7.3)	2 (6.7)	6 (7.1)
Nervous system disorders			
Dizziness	3 (5.5)	0	3 (3.5)
Headache	13 (23.6)	6 (20.0)	19 (22.4)
Respiratory, thoracic and mediastinal disorders			
Cough	6 (10.9)	0	6 (7.1)
Oropharyngeal pain	5 (9.1)	3 (10.0)	8 (9.4)
Skin and subcutaneous tissue disorders			
Pruritus generalized	1 (1.8)	2 (6.7)	3 (3.5)
Rash	2 (3.6)	2 (6.7)	4 (4.7)

Of the 60 patients included in the Safety Population of RODOS-OFU, there was one SAE of hypertensive emergency experienced on the day of the RHODOS-OFU visit, which was over 3 years after completing

treatment with idebenone in RHODOS. The investigator considered this event not related to study drug received in RHODOS. No other relevant safety findings were derived from RHODOS-OFU.

FRDA

In each of the FRDA studies, the majority of subjects had at least one AE (over 90% for all idebenone doses combined and over 80% for placebo). The most common AEs reported in all three double-blind studies (NICOSIA, IONIA and MICONOS) were headache (33.2%), nasopharyngitis (28.5%), diarrhoea (18.8%) and nausea (16%). The incidence of these events was generally similar between idebenone and placebo groups.

Treatment-related AE reported by ≥ 10.0% of subjects on idebenone (all doses combined) and placebo in each of the three studies (NICOSIA, IONIA and MICONOS) were headache and nausea. Other treatment-related AEs reported by ≥ 10.0% of subjects in individual FRDA studies included diarrhoea (16.2%) and dyspepsia (10.8%) in NICOSIA, abdominal pain upper (13.0%) and fatigue (10.9%) in IONIA, and diarrhoea (12.7%) in MICONOS.

Diarrhea and vomiting were reported as treatment-related AEs at a higher incidence in the subjects receiving idebenone compared to subjects receiving placebo in the FRDA studies.

No clear dose relationship for the incidence of AEs or treatment-related AEs was seen.

- NICOSIA

In the Nicosia-FRDA study, the AEs reported by ≥10.0% of subjects on idebenone (all doses combined) at the MedDRA PT level were: upper respiratory tract infection (48.6% of subjects affected), headache (43.2%), myalgia and gastroenteritis (27.0% each), nausea (21.6%), diarrhea (16.2%), dyspepsia (13.5%), fall and white blood cells decreased (10.8% each). The corresponding incidences for these events in the placebo group were: upper respiratory tract infection (36.4%), headache (36.4%), myalgia (18.2%), gastroenteritis (9.1%), nausea (27.3%), diarrhea (0.0%), dyspepsia (1.9%), fall (0.0%) and WBC decreased (27.3%).

The incidence of diarrhoea was higher on idebenone (all doses combined) than placebo (16.2% versus 0%). The incidence of upper respiratory tract infection, headache, myalgia, gastroenteritis, dyspepsia, and falls was higher with active treatment than with placebo but did not appear to be dose-related. Fatigue and pyrexia were more common in the subjects exposed to idebenone (8.1% for both) compared to subjects exposed to placebo (0% for both). These AEs also appeared not to be dose-related. The absolute number of AEs were small in most cases.

The majority of AEs were mild or moderate in intensity, one subject receiving 180/360 mg/day idebenone experienced severe nausea and vomiting and one subject receiving placebo experienced severe angina pectoris. These severe events were considered severe AEs (SAEs).

The incidences of treatment-related headache and diarrhea were notably higher on idebenone (27.0% and 16.2%, all doses combined) compared with placebo (18.2% and 0%).

- IONIA

The AEs reported by ≥10.0% of subjects on idebenone (all doses combined) at the MedDRA PT level were: headache (39.1% of subjects affected), abdominal pain upper (17.4%), nausea, fatigue, pyrexia, upper respiratory tract infection and muscle spasms (15.2% each), diarrhoea, fall, pain in extremity and dizziness (13.0% each), nasopharyngitis, limb injury and pharyngolaryngeal pain (10.9% each). The corresponding incidences for these events in the placebo group were: headache (37.5%), abdominal pain upper (4.2%), nausea, fatigue and pyrexia (12.5% each), upper respiratory tract infection (37.5%),

muscle spasms (8.3%), diarrhoea (12.5%), fall (4.2%), pain in extremity (4.2%), dizziness (12.5%), nasopharyngitis (0%), limb injury (12.5%) and pharyngolaryngeal pain (16.7%).

Consequently, the incidences of abdominal pain upper, upper respiratory tract infection, muscle spasms, falls, pain in extremity and nasopharyngitis were notably higher in the idebenone group (all doses combined) than in the placebo group. Chromaturia was also noted at a higher incidence in subject receiving idebenone compared to subjects receiving placebo (6.5% versus 0%). The incidence in the IONIA extension study was 10.3%. Of these AEs, abdominal pain upper, fall, and chromaturia were more common at the higher idebenone dose. It should also be noted that the absolute number of AEs was limited in most cases.

No SAEs were reported in the 450/900 mg/day idebenone treatment group but three subjects in the 1350/2250 mg/day group reported SAEs (all considered unrelated to treatment) including one case of severe chest pain on two occasions and severe migraine, one case of severe pain in extremity and one case of severe idiopathic thrombocytopenic purpura and severe headache. Furthermore, one subject in the placebo group reported a SAE of dizziness postural considered unrelated to treatment.

The incidence of treatment-related abdominal pain upper and diarrhea was notably higher on idebenone (13.0% and 8.7%, all doses combined) compared with placebo (4.2% for both).

- MICONOS

The AEs reported by ≥10.0% of subjects on idebenone (all doses combined) at the MedDRA PT level were: nasopharyngitis (39.3% of subjects affected), headache (29.5%), diarrhoea (20.8%), nausea (15.0%), back pain (13.3%), vomiting (12.1%) and cough (11.0%). The corresponding incidences for these events in the placebo group were: nasopharyngitis (35.6%), headache (39.0%), diarrhoea (13.6%), nausea (15.3%), back pain (10.2%), vomiting (3.4%) and cough (10.2%). The incidence of vomiting was notably higher on idebenone (all doses combined) than on placebo.

A total of 11 cases of bronchitis were reported. The reporting incidence was higher in idebenone-treated patients (5.7%) compared with placebo (1.6%).

SAEs were reported by 19 subjects on idebenone (11.0%) including 5 subjects each in the 180/360 mg/day idebenone and 450/900 mg/day idebenone treatment groups and 9 subjects in the 1350/2250 mg/day idebenone group. One subject each in the 180/360 mg/day idebenone group (severe visual acuity reduced and fatigue) and 450/900 mg/day idebenone group (severe chest pain) reported SAEs that were considered possibly related to study treatment. Six subjects (10.2%) in the placebo group reported SAEs, a similar incidence to that observed in the idebenone (all doses combined) group. Two subjects had SAEs considered possibly related to study treatment, one case of severe fatigue and anxiety and one case of severe flatulence and abdominal discomfort.

Treatment-related AEs reported by ≥10.0% of subjects on idebenone (all doses combined) at the MedDRA PT level were headache (14.5%), diarrhea (12.7%) and nausea (11.0%). The corresponding incidences for these events on placebo were: headache (27.1%), diarrhea (8.5%) and nausea (13.6%). The incidence of treatment-related nausea and gastroenteritis increased with idebenone dose. Headache was more frequently reported by subjects on placebo than on idebenone. Treatment-related diarrhea, vomiting, back pain, cough and pruritus were more frequently reported by subjects on idebenone (12.7%, 6.4%, 4.6%, 4.6% and 2.3%, respectively) than on placebo (8.5%, 3.4%, 0%, 0% and 0%). The incidence of treatment-related back pain increased with idebenone dose, the others AEs did not.

Comparison of AEs in LHON versus FRDA

The following AEs were reported at a higher incidence in LHON subjects compared to FRDA: LVH was reported by four subjects (7.3%) with LHON receiving idebenone but was not reported in any FRDA

subjects receiving idebenone. Several AEs representing laboratory abnormalities were reported in LHON subjects that had not been reported as AEs in the FRDA subjects but all of these were reported at a similar or higher incidence in the placebo group.

Other AEs observed with a higher incidence in LHON versus FRDA patients were constipation, influenza, alanine aminotransferse increased, blood creatine phosphokinase increased, blood triglycerides increased, cough, oropharyngeal pain, pruritus generalized and rash.

Furthermore, dizziness was reported at a higher incidence in subjects receiving idebenone (5.5%) compared to subjects receiving placebo (0%) in the RHODOS study, but no difference in incidence was observed in the FRDA studies.

Serious adverse event (SAEs) / deaths / other significant events

- Death

No deaths occurred in the RHODOS study and no deaths occurred during the clinical program for FDRA. One patient died of myocardial infarction during the MICONOS-extension study. The investigator assessed the causal relationship between the event and the study drug as unrelated and attributed the event to a pre-existing condition.

- SAEs

SAEs observed in the RHODOS and FRDA studies are described above, for each study separately, in detail.

Two SAEs occurred in the RHODOS study, however, they were considered unrelated to the study drug. In the NICOSIA and MICONOS studies, the incidence of SAEs was lower or similar on idebenone and placebo. The proportions of subjects with SAEs was higher in the MICONOS study compared with the IONIA and NICOSIA studies, which was likely due to the longer duration of the study. Although the IONIA study had an overall higher incidence of SAEs on idebenone compared with placebo, all SAEs were considered unrelated the treatment. Four subjects experienced SAEs during the IONIA extension study, which were considered not related to treatment. During the MICONOS extension study, no treatment-related SAEs were reported.

Laboratory findings

<u>Haematology</u>

There was no evidence observed for an effect over time on any haematology parameter after treatment with idebenone in the RHODOS study. Results for idebenone were generally similar to those with placebo. At Week 4, Week 12 and Week 24, only small mean changes from Baseline were observed in each treatment group. Values for mean corpuscular haemoglobin and mean corpuscular volume above the normal range were the abnormalities most commonly seen in both treatment groups. However, these were also seen at Baseline and may be related to chronic consumption of alcohol, which is known to play an important role in the clinical expression of LHON (Kirkman et al., 2009b).

Cases of low white blood cell counts occurred during the NICOSIA study, but these were evenly distributed between the placebo and idebenone groups, and in all but one case were normal on re-checking at a local laboratory, suggesting that delays in shipping the samples may have been responsible for the findings. However, one case was considered probably related to idebenone use due to positive de-challenge. Furthermore, elevated haemoglobin and haematocrit values were reported for subjects in all treatment groups throughout the study.

No meaningful difference of hematologic parameters such as neutrophils, lymphocytes and white blood cell count was observed during the course of IONIA across active and placebo groups. Normal to high

shifts were more frequent with active treatment than with placebo for three parameters only, red blood cells, hematocrit and haemoglobin, but these findings were not considered clinically significant. In IONIA extension study, there was one case of a slight decrease in the levels of mean corpuscular hemoglobin concentration. A marked drop in the white blood cell count was seen at one visit in two subjects. Both cases were deemed by the investigator as unrelated to the study drug.

In MICONOS, a slight but consistent decrease of leukocytes compared to Baseline in all idebenone study groups was observed. In none of the subjects was the decrease considered clinically notable (i.e. <2 x 109/l).

Biochemistry results

There was no evidence observed for an effect over time on any clinical chemistry parameter after treatment with idebenone in RHODOS. Results for idebenone were generally similar to those with placebo. At Week 4, Week 12 and Week 24, only small mean changes from Baseline were observed in each treatment group. A number of subjects had individual clinical chemistry values that were outside the laboratory normal range. However, the numbers with abnormal values were similar at Baseline and after treatment and were also generally similar for idebenone and placebo.

Triglyceride value above the normal range was the most commonly seen abnormality, seen already at Baseline in both treatment groups. Other noteworthy abnormalities included high levels of gamma-glutamyl transferase (GGT) and transaminases, which were also seen at Baseline. There were 3 abnormal values observed at Baseline, compared to 3 abnormal values at the end of treatment in idebenone treated patients. One patient had an abnormal (>3xULN) aspartate aminotransferase (AST) level at Baseline, which was normal at the end of treatment, and one patient who had a normal AST level at Baseline, presented with an abnormal AST level (>5xULN) at the end of treatment. However, this patient also presented with an abnormal GGT level at Baseline, thus indicating a high likelihood to have a pre-existing medical hepatic issue. Another idebenone-randomised patient presented with abnormal alanine aminotransferase (ALT), AST and GGT at both Baseline and end of treatment. One patient discontinued the RHODOS study because of abnormal liver function test.

In the NICOSIA study, there were few reported electrolyte values and values for glucose, albumin, bilirubin, protein, and for AST, ALT and creatine kinase outside the normal ranges in idebenone-treated subjects. The incidences were comparable to those seen in the placebo group, and no dose-dependent trends were observed. There were a number of high values for lactate dehydrogenase reported in all treatment groups. However, there was no difference between the combined idebenone-treated group and the placebo group. High uric acid was reported more frequently on idebenone than on placebo, but was not considered of clinical significance.

There were no clinically relevant changes over time for any biochemistry parameters in the IONIA study, with mean values generally being within the respective normal ranges at baseline and over the 24-week treatment period. Some small changes of interest, albeit non-clinically significant, were noted for albumin levels, AST, and creatine kinase. In the IONIA extension study, mean values of glucose remained generally stable but 6 subjects (9%) experienced a drop in glucose levels of at least 2 mmol/L during the course of this study. Each of these subjects had also received treatment with idebenone during the IONIA study.

There were no noteworthy findings for changes in biochemistry parameters or for shifts in biochemistry parameters in the MICONOS study. No drug related clinically significant haematology abnormalities were seen. There were no subjects with AST levels >3 times ULN (upper limit of normal) and only one subject on placebo with ALT levels >3xULN. There were some notably abnormal values observed for bilirubin (both with idebenone and placebo), creatinine (idebenone only) and creatinine clearance (idebenone

only) in a few subjects but for the most part values for these subjects were also notably abnormal at screening or Baseline.

Urinalysis results

There was no evidence observed for an effect of idebenone treatment on urinalysis in the RHODOS and IONIA study.

In NICOSIA, there were no significant findings in urinalysis other than the occurrence of pink tinged urine reported as a possibly treatment-related AE of chromaturia for one subject in the 450/900 mg/day group, and cloudy urine observed in another subject in the 180/360 mg/day group.

In IONIA, 4 subjects receiving idebenone experienced chromaturia, which were considered clinically significant laboratory abnormalities.

There were no noteworthy findings for changes in urinalysis parameters in the MICONOS study.

No clinically significant changes over time were observed in the extension studies.

Vital signs

There were no significant changes in vital signs reported.

Safety in special populations

Special populations have not been specifically studied.

Safety related to drug-drug interactions and other interactions

No clinical drug-drug interaction studies have been performed in support of this Application and no case reports of drug interactions have been received from post-marketing data.

A number of *in vitro* studies have been performed to assess the effects of idebenone and its structurally-closest related metabolite QS10. The results are presented and discussed in section 2.4. In summary, the data showed that idebenone and its metabolite QS10 do not exert systemic inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 at clinically relevant concentrations of idebenone or QS10. In addition, no induction of CYP1A2, CYP2B6 or CYP3A4 was observed. However, inhibition of P-gp with possible exposure increases of of P-gp substrates..

Discontinuation due to adverse events

One subject withdrew from the RHODOS study due to abnormal liver function test results, which occurred after 35 days of treatment start with idebenone 900 mg/day and were severe in intensity and considered possibly related to treatment.

No subjects discontinued the NICOSIA or IONIA studies prematurely due to an AE. However, in the IONIA extension study, two subjects with SAEs withdrew due to pregnancy and general poor health (reason for withdrawal was recorded as other), respectively. Additionally, one subject had discontinued study treatment for an AE of disorientation but was withdrawn from the study due to poor compliance. In the MICONOS study, the number of subjects who permanently discontinued study drug due to AEs was low, with a similar percentage of subjects discontinuing on idebenone (2.9%, 5 subjects) and placebo (3.4%, 2 subjects). Amongst these subjects, there was none who discontinued treatment on the highest idebenone dose (1350/2250 mg/day), but one subject (1.8%) on 450/900 mg/day and 4 subjects (7.0%) on 180/360 mg/day idebenone dicontinued. The higher frequency of AEs leading to study drug discontinuation in the 180/360 mg/day idebenone group was mainly due to the occurrence of pregnancy in two subjects. Other AEs leading to discontinuation included gastrointestinal events (e.g. nausea, diarrhea, vomiting and gastritis) and supraventricular extrasystoles in the active treatment groups.

Supraventricular extrasystoles was also reported as a SAE, but was not considered by the investigator to be related to study treatment.

Post marketing experience

Post-marketing data were available from Takeda Pharmaceuticals for Mnesis, 45 mg idebenone oral tablet, intended for the treatment of degenerative and vascular cognitive disorders, including Alzheimer's disease. The patients population exposed to idebenone from 1 April 2004 to 31 March 2013 was estimated at approximately 130,784 patient-years. As of end of December 2013, 57 AEs (21 serious and 36 non-serious) were reported mainly from Switzerland and France. Of the serious reports, one described fulminant hepatitis and multi-organ failure in a 40-year old male subject with FRDA. The events occurred more than 4 years after initiation of therapy with idebenone. The subject had a medical history of severe hypertrophic cardiopathy and was taking numerous concomitant medications including acetylsalicylate lysine, spironolactone, baclofen, bisoprolol fumarate, perindopril, alprazolam, paroxetine and macrogol. Additionally, a poorly documented case of cytolytic hepatitis was reported for a 20-year-old male patient who was treated with Mnesis (idebenone) 7 mg/kg for FRDA.

In addition, post-marketing data were available from the Canadian market where Santhera used to market idebenone for FRDA. In addition, in September 2009, Santhera started a Named Patient supply program (NPP) which ensures the distribution of idebenone. In Canada, Santhera marketed idebenone 150 mg oral tablets, under a Notice of Compliance with Conditions for the indication of symptomatic management of patients with Friedreich's Ataxia between July 2008 and April 2013, when the product was withdrawn from the market due to the failure of further clinical trials confirming efficacy. As of end of April 2013, 118 AEs were reported from Canada, of which 28 were serious and 90 were non-serious. The AEs most frequently reported were minor gastrointestinal events such as nausea, vomiting, diarrhea and abdominal pain.

Expanded Access Program (EAP)

During the course of the assessment, the Applicant provided an updated EAP report (clinical cut off on 20 March 2015) including 93 patients in the safety population. Of these, 76 had received Raxone treatment for at least 6 months and 53 for at least 12 months. The maximum treatment period was 36 months (2 patients) and the mean treatment duration was 13.3 (range 0- 36.2) months. For a summary of demographics and baseline characteristics, see section 2.5.3.2.

There were no deaths in the EAP. A total of 17 AEs were reported from 10 patients. The most frequently reported AE was mild diarrhoea. The severity of reported AEs were classified as mild (65%), moderate (24%) or unknown (11%). Four AEs in three patients were classified as serious. The four SAEs were osteonecrosis, bipolar disorder, adenoid cystic carcinoma and pneumonia. All four SAEs were considered by the treating physician and by the Applicant as not related to Raxone treatment.

Five (5) AEs in 4 patients were classified as being related to Raxone treatment by either the reporting physician or by the Applicant. These five events were nausea and headache, hepatic enzyme increased, diarrhoea and white blood cell count decreased in one patient each.

2.6.1. Discussion on clinical safety

The main support for the safety assessment of this Application was derived from RHODOS and its extension RHODOS-OFU investigating the efficacy and safety of Raxone in the treatment of LHON's disease. Additional safety information was available from three Phase III trials in Friedreich's ataxia (FRDA), another rare mitochondrial disease, and two related open-label extension studies. The proposed dose recommendation for LHON (900 mg/day, 2x150mg tablets t.i.d.) was comparable to the doses used

in the FRDA studies (180-2250 mg/day) and hence, data from the FRDA clinical program were considered supportive. Taken together, LHON and FRDA studies compromised safety data in 242 patients exposed to ≥900 mg/day idebenone. Duration of exposure was 6 months in the RHODOS study, up to 12 months in the FRDA studies and in open-label studies up to 24 months.

Furthermore, post marketing data were available from FRDA subjects and Alzheimer patients treated with idebenone from Canada, Switzerland and France. Safety data were also available from the EAP.

From a demographic point of view, the population studied in RHODOS was considered by the CHMP to be representative of the population suffering from LHON. However, although explained by the rarity of the disease, the low patient exposure to idebenone in RHODOS (55 patients with LHON treated for 6 months) provided limited safety data in the target population. Furthermore, only limited information was available for the safety of long-term use of idebenone, which was consequently considered missing information in the RMP. Of the 93 patients in the safety population of the EAP, 53 had received idebenone treatment for at least 12 months.

The lack of studies in specific populations including patients with renal and hepatic impairment was considered acceptable by the CHMP given the overall benign safety profile of idebenone and the rarity of the target disease. Nevertheless, in the product information, caution was advised in treatment of patients with hepatic or renal impairment. In addition, use in pregnancy and lactation, patients under 14 years of age, the elderly, and patients with hepatic and renal impairment were reflected as missing information in the RMP.

Overall, the incidence of AEs and treatment related AEs were low and similar between idebenone and placebo groups. The most common AEs in the idebenone treatment group were headache, nasopharyngitis, diarrhea and nausea. The majority of AEs were mild or moderate in intensity.

With respect to the RHODOS study, headache (23.6%), nasopharyngitis (25.5%), dizziness (5.5%) and cough (10.9%) were more frequent in the idebenone group than the placebo group. In addition, five subjects (four treated with idebenone and one treated with placebo) experienced treatment-related AEs: blood triglycerides increased (reported for one subject in each group); left ventricular hypertrophy (LVH), Wolff-Parkinson-White syndrome, and liver function tests abnormal.

The total reporting incidence of LVH was 7.3% (4 patients) in the idebenone group versus 0.0% in the placebo group, although only one case was considered related to the treatment by the investigator. All events were non-serious and were reported by the same investigational site on the basis of the ECG readings. The diagnosis was not supported by clinical or ultrasound evidence. A further review of all the ECG reports showed that the cardiologist at this site reported findings suggestive of LVH in 16 additional cases. Most of them were detected pre-treatment at Baseline. The incidence of ECG findings suggestive of LVH developing after initiation of the study treatment was lower in the idebenone group (7.27%) than in the placebo group (13.33%). Comparison of a single baseline ECG to a single ECG at 6 months is not a robust determination of cardiac safety and caution should be used in interpreting these data. Taking together all available data in 350 patients with FRDA and in 85 patients with LHON, there was no demonstrated signal of any ECG abnormality in heart rate, AV conduction as measured by the PR interval, depolarization as measured by the QRS interval nor in cardiac repolarization as defined by the QTcF duration attributable to idebenone. Hence, the CHMP concluded that there was no firm evidence of cardiac disorders associated with idebenone use.

Blood triglycerides increased was reported for one subject in each treatment group, whereby the patient in the placebo arm also reported the treatment-related AE alanine aminotransferase increased.

Concerning the treatment related AE of Wolff-Parkinson-White syndrome, the patient already had an ECG abnormality at screening, reported as incomplete left bundle block. This finding was further elaborated by

an independent ECG reading and medical evaluation performed by a contract research organisation, which classified a ventricular conduction defect of the ventricular pre-excitation pattern (Wolff-Parkinson-White type) both for the pre-treatment as well as for the on-treatment ECG. General ECG abnormalities, including Wolff-Parkinson-White syndrome, are not uncommon in LHON patients as reported in the literature (Bower et al., 1992; Nikoskelainen et al., 1994; Finsterer et al., 2001; Sorajja et al., 2003). For these reasons, the CHMP considered that the reported treatment related AE was likely unrelated to idebenone use.

Treatment-related AE reported by ≥10.0% of subjects in the FRDA studies (NICOSIA, IONIA and MICONOS) were headache and nausea. Other treatment-related AEs reported by ≥ 10.0% of subjects in individual FRDA studies included diarrhoea and dyspepsia (10.8%) in NICOSIA, abdominal pain upper (13.0%) and fatigue (10.9%) in IONIA, and diarrhoea (12.7%) in MICONOS. Diarrhea and vomiting were reported as treatment-related AEs at a higher incidence in the subjects receiving idebenone compared to subjects receiving placebo in the FRDA studies. Furthermore, in the MICONOS study treatment-related back pain was more frequently reported by subjects on idebenone (4.6%) than on placebo, and the incidence increased with idebenone dose. There was also an increase in the incidence of reports of bronchitis (5.7%) in the idebenone groups in MICONOS compared to placebo. In another FRDA study (IONIA) an increased incidence of pain in extremity (13%) was observed in the idebenone groups compared to the placebo group including one severe case reported as a SAE. Diarrhea is a known adverse drug reaction of idebenone and was included in SmPC section 4.8. Furthermore, based on the above data, the CHMP was of the view that a causal relationship to idebenone use could not be excluded for the AEs of vomiting, nausea, dyspepsia, back pain, pain in extremity and bronchitis.

No deaths occurred in the RHODOS study and during the clinical program for FRDA. One patient died of myocardial infarction during the MICONOS-extension study. The causal relationship between this event and the study drug was regarded as unrelated and to be attributed to the patient's underlying disease.

Chromaturia and blood dyscrasia were reported as laboratory abnormalities in FRDA studies. Although these laboratory findings were not observed in patients with LHON, the CHMP considered that a warning statement should be included in the product information to inform healthcare professionals and patients that the metabolites of idebenone are coloured and may cause discoloration of the urine. With regards to haematological changes, the Applicant submitted a detailed analysis which indicated that the AEs related to blood count abnormalities were unlikely related to idebenone and rather related to multiple confounding factors present in the study population (i.e., FRDA but not LHON patients). Nevertheless, an uncertainty remained and blood count abnormalities were included as an important potential risk in the RMP.

Data from RHODOS indicated that 3 subjects had increased liver enzymes within the study and one of the patients discontinued the study because of this AE. However, on closer examination all 3 subjects had values higher than normal already at Baseline. Data from FRDA subjects showed very few categorical changes for liver enzyme levels from <3xULN to >3xULN or >5xULN and no clinically significant change in liver function tests was observed with idebenone treatment. However, a report of fulminant hepatitis and another report of cytolytic hepatitis were received in the context of post marketing monitoring. Both reports were inconclusive since the subject with fulminant hepatitis had multiple concomitant medications which were known to be potentially hepatotoxic agents thus representing important confounding factors, while for the case of cytolytic hepatitis a coherent causal assessment could not be made due to the lack of information. Taken together, the available data did not present firm evidence for a causal relationship of liver enzyme increases and hepatitis with idebenone use, however, at the same time a causality could not be excluded without doubt, also considering that the product information of the reference product Mnesis lists these events as ADRs. Therefore, abnormal liver function and hepatitis was included as an

important potential risk in the RMP. Furthermore, the CHMP and the PRAC were of the view that additional data should be collected in a post-marketing study to further elucidate this potential risk.

No interaction studies in humans have been performed. Given the results from *in vitro* inhibition data, presystemic inhibition of CYP3A4 by idebenone could not be excluded. Therefore, the CHMP requested that the Applicant should perform an *in vivo* post-authorisation study to assess the potential PK interaction of idebenone with midazolam in healthy male volunteers, as discussed in detail in section 2.4.

Spontaneous abortion seemed to be higher than expected with 4 out of 8 cases of drug exposure during pregnancy including reports from post-marketing monitoring resulting in spontaneous abortion. All cases reported were for patients with FRDA and some cases were confounded by the use of concomitant medications. Taken together and including observations in the literature, the CHMP was of the view that there was insufficient evidence to conclude on a causal relationship with idebenone.

AEs observed in the EAP were in accordance with AEs observed in the RHODOS and FRDA studies. Only very limited information could be derived from RHODOS OFU. No new safety concern arose from these data.

Finally, the CHMP noted that in principle the SmPC content for a hybrid product should be consistent with the reference medicinal product. Mnesis, the reference product of Raxone, is administered at doses of 90 mg/day idebenone, which is 10 times less than the recommended daily dose for Raxone. Therefore, the CHMP considered that ADRs listed for Mnesis should also be reflected in SmPC section 4.8 of Raxone. The following ADRs are listed for Mnesis:

- Hypersensitivity reactions: rash, pruritus
- Psychoneurological reactions: convulsions, delirium, hallucinations, excitation, involuntary movements, hyperkinesia, poriomania, dizziness, headache, restlessness, light-headedness, torpor.
- Gastro-intestinal disorders: nausea, vomiting, anorexia, stomach ache, diarrhoea.
- Blood disorders: agranulocytosis, anaemia, leukocytopenia, thrombocytopenia
- Hepatic disorders: increased aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, and gamma-glutamyl transferase or bilirubin.
- Kidney disorders: increased azotaemia
- Metabolic disorders: increased total cholesterol or triglycerides
- General: Malaise

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the product information. Hypersensitivity to the active substance or to any of the excipients was included as a contraindication in line with the SmPC guideline.

Additional safety data needed in the context of a marketing authorisation under exceptional circumstances

Taking into account the totality of the available data, the CHMP was of the view that the data set on the clinical safety of Raxone under normal conditions of use could not be considered comprehensive, nor was it considered feasible to generate a comprehensive data set mainly due to the rarity of LHON's disease. Furthermore, at the time of this report, idebenone was already used to treat LHON patients in clinical practice, thus preventing the generation of placebo-controlled data to confirm the safety profile as established based on the available data at the time of this report.

Following an oral explanation by the Applicant, the CHMP agreed that it was not feasible to produce a comprehensive data set under normal conditions of use of Raxone. The CHMP was furthermore of the view that a marketing authorisation under exceptional circumstances should be granted subject to a number of specific obligations in line with a program of studies proposed by the Applicant. Within this program, additional safety data should be collected through a Product Exposure Registry. Data from this registry should be generated on a regular basis based on an agreed protocol and should also aim at addressing the safety concerns as specified in the RMP. In addition, while mainly intended for the generation of further efficacy data, additional safety information should also be generated from an open label interventional study in LHON patients treated with idebenone as well as from follow-up data from the ongoing EAP (see section 2.5.5.). The specific obligations will be reviewed annually and continuation of the authorisation shall be linked to these annual re-assessments.

2.6.2. Conclusions on the clinical safety

The CHMP was of the opinion that the available safety data, including clinical data from LHON patients as well as supportive data from the FRDA clinical program and post-marketing experience, supported the Application for Raxone in the treatment of visual impairment in adolescent and adult patients with LHON's disease. The safety profile was considered rather benign with only few reports of serious AEs and the majority of AEs being mild or moderate in intensity. Relevant safety data have been adequately reflected in the product information as well as the RMP.

With regards to the submission of periodic safety update reports (PSURs), the CHMP considered that the first PSUR for Raxone should be submitted within 12 months following authorisation in the EU. Thereafter, the requirements of the list of Union reference dates (EURD list) apply.

Nevertheless, the available safety data in the target population were limited and considered by the CHMP to be incomprehensive. The CHMP therefore considered the following measures necessary to generate additional safety data in the context of a marketing authorisation under exceptional circumstances:

- 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. The registry should also be used to generate data on long-term effectiveness.

2.7. Pharmacovigilance

The CHMP considers that the Pharmacovigilance system as described by the Applicant fulfils the requirements and provides adequate evidence that the Applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

2.8. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.2 was acceptable providing minor revisions were made to the RMP. The applicant addressed these minor revisions and submitted an update RMP version 1.3.

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

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 Use in elderly patients Use in patients with hepatic impairment Use in patients with renal impairment Safety on long-term use of Raxone in patients with LHON Potential for pre-systemic inhibition of CYP3A4 Potential for inhibition of P-gp

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
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 therapeutic response • To further elucidate the risk of abnormal liver function tests and hepatitis	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	Planned	Submission of Protocol: 30 November 2015 Reports to be submitted with annual re-assessments.
Phase I open label	Primary	Potential for	Planned	Final study

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
study of the potential pharmacokinetic interaction of idebenone (150 mg film-coated tablet) with midazolam in healthy male volunteers Category 3	• To evaluate the pharmacokinetics of midazolam in the presence of idebenone after repeated administration of idebenone as a film-coated tablet. <u>Secondary</u> • To obtain further safety and pharmacokinetic information after repeated administration of idebenone.	pre-systemic inhibition of CYP3A4		report: 31 January 2017

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Potential risk: Abnormal liver function test and hepatitis	SmPC Prescription only medicine Treatment should be initiated and supervised by a physician with experience in LHON	None
Potential risk: Blood count abnormalities	SmPC Prescription only medicine Treatment should be initiated and supervised by a physician with experience in LHON	None
Missing Information: Use in pregnancy and lactation	SmPC Prescription only medicine Treatment should be initiated and supervised by a physician with experience in LHON	None
Missing Information: Use in the elderly	SmPC Prescription only medicine Treatment should be initiated and supervised by a physician with experience in LHON	None
Missing Information: Use in children under 14 years of age	SmPC Prescription only medicine Treatment should be initiated and supervised by a physician with experience in LHON	None
Missing Information: Use in patients with hepatic impairment	SmPC Prescription only medicine Treatment should be initiated and supervised by a physician with experience in LHON	None
Missing Information: Use in patients with renal impairment	SmPC Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Treatment should be initiated and supervised by a physician with experience in LHON	
Missing Information: Safety on long term use of Raxone	None	None
Missing Information: Potential for Pre-systemic inhibition of CYP3A4	SmPC Prescription only medicine Treatment should be initiated and supervised by a physician with experience in LHON	None
Missing Information: Potential for inhibition of –P-gp	SmPC Prescription only medicine Treatment should be initiated and supervised by a physician with experience in LHON	None

2.9. Product information

Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Raxone (idebenone) is included in the additional monitoring list as it is approved under exceptional circumstances.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the Applicant showed that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

Beneficial effects

LHON patients suffer from sudden, rapid and severe bilateral vision loss, which is irreversible in most patients following degeneration of the optic nerve in the late, chronic stage of the disease. Effective treatments should aim at preventing or reversing loss of vision. At the time of this report, there was no approved treatment available.

The benefits of Raxone in the treatment of LHON's disease have been investigated in the double-blind, placebo controlled RHODOS trial in which patients were treated with 900mg idebenone (2x150mg t.i.d.) or placebo over a period of 6 months. Further supportive data was available from an Expanded Access Programme (EAP), a Natural History Case Record Survey (CRS) and the scientific literature.

Overall, and across all available data sets, there was a consistent pattern of visual improvements in favour of Raxone. In RHODOS, there was a numerical advantage of Raxone over placebo throughout the different visual acuity (VA) endpoints. For the key secondary endpoint (change in Best VA at Week 24 compared to Baseline), patients in the placebo group worsened by 4 letters on a vision chart, while

patients on idebenone showed a slight improvement by 1 letter. The between-group difference was increased from 5 to 8 letters when analyses were performed on the mITT population (ITT p=0.078 and mITT p=0.015). A beneficial effect in favour of Raxone was also observed for patients with off-chart vision at Baseline, who improved to on-chart vision, being able to read at least 1 line on a vision chart, by the end of the study (7 out of 25 patients in the idebenone group versus 0 out of 13 patients in the placebo group). This change from off-chart to on-chart vision was considered by the CHMP to be clinically meaningful since it represents an important categorical change. Finally, amongst the post-hoc VA analyses, the CHMP considered the responder analysis of clinically relevant recovery (CRR) as defined by Carelli et al. (2011) to be a valuable marker for assessing treatment benefits. A higher proportion of patients in the Raxone group (16/53 patients, 30.2%) than in the placebo group (ITT: 3/29 patients, 10.3%, mITT: 2/28 patients, 7.1%) had CRR in at least one eye. The between-group difference was statistically significant when analyses were conducted on the mITT population (p=0.0234).

In order to compare the data from RHODOS, the EAP and the CRS, additional CRR analyses were conducted. Throughout these analyses there was generally a larger proportion of responders treated with idebenone compared to untreated or placebo-treated patients. After 6 months, 19 out of 62 patients (30.6%) in the EAP had CRR and 18 out of 94 patients (19.1%) in the CRS had spontaneous CRR, which was within the range of the results observed in RHODOS, thus providing independent support of the RHODOS findings. Also, the CRS represented a rather unique dataset contributing to a better understanding of the natural course of LHON's disease.

To some degree, results on VA endpoint in RHODOS were also supported by favourable trends in non-VA endpoints, including improvements of colour contrast sensitivity and preservation of the retinal nerve fibre layer in patients with more recent disease onset, although the sample sizes for these analyses were small.

Finally, while some subgroup analyses in RHODOS suggested a larger effect size of Raxone in patients with disease onset of less than one year, responder analyses in the EAP showed that, in absolute terms, the outcome VA for early versus late-treated eyes was similar. Therefore, and since the current knowledge of the course of the disease suggests that recovery of vision is possible even years after symptom onset, the CHMP considered that the indication should be kept broad and not be restricted to early treatment, as initially proposed by the Applicant. Likewise, only few data were available for paediatric patients treated with Raxone, in particular for patients below the age of 14 (6 patients in the EAP). Nevertheless, taking into account the rarity of the disease and the amount of data that can reasonably be expected to be generated in this age group, the CHMP was of the view that the available data justified an indication in adolescents.

Uncertainty in the knowledge about the beneficial effects

The analysis of RHODOS data was complicated by the small number of study participants and, at the same time, the heterogeneity of the patients enrolled, being at different stages in their disease progression. To a degree, these factors might explain the failure of the RHODOS study to demonstrate superiority of Raxone over placebo in the primary as well as the majority of secondary endpoints at a statistical significance level of 5%. While numerical trends in favour of Raxone were observed, it was difficult to derive firm conclusions from RHODOS alone.

Uncertainties in the robustness of the RHODOS data also arose from the effect of the exclusion of one patient from the placebo group, considered by the Applicant to be a natural history confounder, which resulted in a considerable increase of the between-group differences. In addition, given the potential of spontaneous recovery in LHON's disease, there was a risk of over-estimating the effect of idebenone. Furthermore, many of the subgroup and responder analyses conducted in RHODOS were either based on small sample sizes or lacked pre-specification. Finally, any potential improvement in vision in patients

treated with Raxone did not appear to be translated into benefits for the patient's daily activities and health-related quality of life, although this might be explained by a lack of sensitivity of the HRQoL questionnaire.

For the present Application, independent evidence for efficacy of Raxone was provided from the EAP and the CRS. Comparison to RHODOS was however hampered by the lack of continuous VA measurements as well as the heterogeneous study population. This concern was addressed by the conduct of additional responder analyses abandoning the concept of nadir and differentiating between off-chart and on-chart vision as well as study duration. The analyses across data sets generally supported a beneficial effect of Raxone. In the interpretation of the results it has to be kept in mind that response rates following different response definitions are highly correlated by nature.

During the assessment, questions were also raised about the impact of possible confounding factors, including possible prognostic criteria for spontaneous recovery, such as time since disease onset, mutation status, age and smoking. However, univariate analysis only showed that the T14484C mutation was associated with a higher proportion of CRR responders, which was expected due to the more benign course of the disease in patients with this mutation.

With regards to maintenance of the treatment effects, the results of a single follow-up visit of patients previously treated in RHODOS suggested that the benefits obtained from Raxone treatment over 6 months persisted even after treatment discontinuation. However, hardly any new information for idebenone treatment duration could be derived from these data. Remarkably, when considering the evidence across data sets, there was a higher proportion of patients/eyes with CRR amongst untreated patients after 36 months, compared to treated patients after 6 months. Thus, and despite the availability of data from 45 patients in the EAP who were treated for a prolonged period of time (more than 12 months), uncertainties remained with regards to the benefits of idebenone treatment beyond 6 months. Consequently, the CHMP recommended that the Applicant should gather long-term data post-marketing.

Risks

Unfavourable effects

The most common adverse drug reactions were nasopharyngitis, cough, diarrhoea and back pain.

No serious adverse events have been reported as related to idebenone exposure. Overall, the incidence of adverse events and treatment related adverse events in clinical trials were low and similar between idebenone and placebo groups. The majority of adverse events were mild or moderate in intensity. Furthermore, discontinuations from study drug due to adverse events were generally low. One patient discontinued the RHODOS study because of an abnormal liver function test.

No potential safety signal emerged from the review of vital signs and laboratory data. Chromaturia was reported as laboratory abnormalities in clinical trials in Friedreich's ataxia, which provided supportive evidence for the safety of idebenone at doses recommended for use in LHON. Although these laboratory findings were not observed in LHON patients, a warning was included in the product information to inform healthcare professionals and patients that the metabolites of idebenone are coloured which may lead to discoloration of the urine.

Overall, idebenone at therapeutic doses was well-tolerated and adverse events were generally manageable.

Uncertainty in the knowledge about the unfavourable effects

Limited safety data were available for the target population and for long-term use of Raxone. Furthermore, no specific studies have been conducted in special populations, e.g. renal impairment,

elderly, pregnancy and lactation. However, data from the clinical trials program in Friedreich's ataxia provided supportive information for the safety profile of idebenone. The CHMP was furthermore of the view that the lack of studies in special populations could be accepted due to the generally benign safety profile of Raxone. There was also some post-marketing experience albeit in different populations and at different doses.

Left ventricular hypertrophy was reported as treatment related in one patient receiving idebenone in RHODOS, but the diagnosis was not considered very robust as it was based on ECG readings alone. Furthermore, one patient in the idebenone arm of RHODOS was reported with treatment-related Wolff-Parkinson-White syndrome, but further investigations revealed that a ventricular conduction defect was already present prior to treatment. Taking together the totality of the available safety data including the result from non-clinical tests, there was no evidence for an association of cardiac disorders with idebenone use.

Events of blood dyscrasias have been reported in studies in Friedreich's ataxia. Although these events were most likely related to multiple confounding factors present in that particular population, an uncertainty remained and blood count abnormalities were included as an important potential risk in the RMP.

Three patients in RHODOS had increased liver enzymes and one of the patients discontinued the study because of this event. However, on closer examination all 3 subjects had values higher than normal already at Baseline. Additional post-marketing reports of hepatitis were inconclusive. Taken together, the available data did not present firm evidence for a causal relationship of liver toxicity with idebenone use. However, as an association could not be excluded without doubt, abnormal liver function and hepatitis was included as an important potential risk in the RMP and additional data should be collected post-marketing.

Finally, no interaction studies in humans have been performed and given the results from *in vitro* inhibition data, pre-systemic inhibition of CYP3A4 by idebenone could not be excluded. Therefore, a post-authorisation study to assess potential PK interaction of idebenone with midazolam was included as a requirement in the RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

At the time of this report, there was no approved treatment available for LHON's disease. Thus, there was an unmet medical need for therapies able to prevent or reverse vision loss.

Taking into account the totality of the available data, there was a consistent trend towards a beneficial effect of Raxone in the treatment of vision impairment in LHON patients across data sets. Compared to placebo, patients receiving Raxone treatment over 6 months could read 5-8 letters more (best VA), which represents ≥1 line on a vision chart. Clinically relevant recoveries of vision were observed more frequently in patients treated with Raxone (30%) than in patients receiving placebo (7-10%) or no treatment (19%), suggesting that some patients may derive non-negligible benefits from Raxone.

At the same time, the safety profile of Raxone can be considered benign. Adverse events observed during treatment were generally mild or moderate in intensity. All adverse reactions were manageable and unlikely to require treatment discontinuation.

Benefit-risk balance

The CHMP considered that the observed consistent pattern of visual improvements under Raxone treatment translated into a clinically relevant benefit in the treatment of LHON's disease. Independent

evidence from the EAP and CRS provided reassurance that the trends observed in RHODOS in favour of Raxone were no chance findings. Therefore, and in light of the benign safety profile, the CHMP considered that the benefits of Raxone in the treatment of visual impairment in adolescent and adult patients with Leber's Hereditary Optic Neuropathy outweighed its risks. The CHMP therefore concluded that the benefit-risk balance was positive.

Discussion on the benefit-risk balance

This Application concerned a hybrid version of idebenone, film-coated tablets. The reference product Mnesis is indicated for the treatment of cognitive and behavioural deficits due to cerebral pathologies of vascular or degenerative origin.

LHON is a maternally inherited disease resulting in a defect of the mitochondrial function which in turn causes inactivation and subsequent degeneration of retinal ganglion cells (RGCs). Idebenone, being a derivative of co-enzyme Q10, has been tested in the treatment of various mitochondrial respiratory chain disorders due to its antioxidative and electron carrier properties. A plausible biological explanation for a treatment effect in LHON could be restoration of mitochondrial function during the time window when RGCs are inactive but still viable, thus allowing recovery of vision or prevention of disease progression.

Studies in LHON's disease are challenging due to the rarity of the disease and slow recruitment of patients as well as the occurrence of spontaneous recoveries in a heterogeneous population. The pivotal trial supporting this Application, RHODOS, failed to show superiority of Raxone over placebo at a statistical significance level of 5% and there were concerns questioning the robustness of the trial's data in general. These concerns were alleviated by additional adequately designed analyses including independent evidence from the EAP and natural history CSR, confirming the trends observed in RHODOS towards a favourable effect of idebenone treatment. This was further substantiated by the Applicant in an oral explanation. Altogether, the totality of the evidence allowed the CHMP to conclude that LHON patients may gain clinically relevant benefits from Raxone treatment.

Due to limitations of the available data at the time of this report, the CHMP requested additional data on the efficacy and safety of long-term treatment with Raxone as well as to investigate pre-systemic PK interactions post-marketing. Data collection post-authorisation should also be used to further elucidate a potential unconfirmed risk of liver enzyme increases and hepatotoxicity. As only few patients had been exposed to Raxone for more than 6 months, no recommendations could be given on the treatment duration, and post-marketing data should aim at addressing this issue.

The CHMP furthermore considered that the safety and efficacy in patients 12 years of age and younger had not been established and therefore approval was limited to adults and adolescents. Treatment should be initiated and supervised by physicians with experience in LHON.

Marketing authorisation under exceptional circumstances

Taking into account all available data, the CHMP considered that the benefit-risk balance of Raxone in the treatment of visual impairment in adolescent and adult patients with LHON was positive. However, the CHMP was of the view that the data set on the clinical efficacy and safety of Raxone could not be considered comprehensive. In an oral explanation, the Applicant convincingly demonstrated that, due to the rarity of LHON's disease and since idebenone was already used to treat LHON patients in clinical practice, it was not feasible to recruit sufficient patients within a reasonable timeframe into a placebo-controlled trial, thus preventing the generation of additional controlled data to confirm the outcomes observed in RHODOS, the EAP and the CRS. However, the Applicant proposed a program of both interventional and non-interventional studies to generate additional data post-marketing.

The CHMP agreed that it was not feasible to produce a comprehensive data under normal conditions of use of Raxone due to the rarity of the indication. The CHMP was furthermore of the view that a marketing authorisation under exceptional circumstances should be granted subject to a number of specific obligations:

- In order to further investigate the benefits of Raxone in the treatment of LHON patients, the MAH should conduct and submit the results of an external natural history controlled, open-label intervention study to assess the efficacy and safety of Raxone in the treatment of LHON patients, including long-term treatment.

  A draft protocol was reviewed by the CHMP during the course of this Application. Both patients/eyes with newly diagnosed disease (≤1 year), but also to those presenting >1 and up to 5 years since onset of symptoms should be recruited. Patients should receive Raxone treatment up to 24 months. The planned number of patients to be recruited (n=250, 125 each for disease onset ≤ and > 1 year prior to study star) was considered large enough. Patients form the open-label study should be matched to historic controls based on pre-specified criteria. Any substantial change(s) to the protocol should be agreed with the CHMP in advance. Furthermore, a summary of all protocol amendments should be presented with the annual re-assessments.

  Finally, while mainly intended for the generation of efficacy data, additional safety information should also be generated from this study. The final study report should be provided by 31 August 2020.

- In order to further investigate the benefits of Raxone in the treatment of LHON patients, the MAH should maintain and extend the Historical Case Record Survey of Visual Acuity Data from Patients with LHON to serve as the external control to the open label study.

  The protocol was reviewed by the CHMP during the course of this Application. Any substantial change(s) to the protocol should be agreed with the CHMP in advance. Furthermore, a summary of all protocol amendments should be presented with the annual re-assessments.

  The final report should be provided by 31 August 2020.

- Non-interventional post-authorisation safety study (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. The registry should also be used to generate data on long-term effectiveness.

  While mainly intended for the generation of further safety data, data on long-term effectiveness and lack or loss of therapeutic response should also be generated from the drug exposure registry. Data from this registry should furthermore aim at addressing safety concerns including hepatotoxicity as specified in the RMP.

- The MAH should follow up patients in the existing Expanded Access Programme and submit the final results.

  Follow-up was planned until no longer required for named-patient access, which was estimated at 3 years. While mainly intended for the generation of further efficacy data, additional safety information should also be generated. The final study report should be provided by 31 August 2019.

Data from these studies should be generated on a regular basis for review in the context of the annual re-assessments.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Raxone in the treatment of visual impairment in adolescent and adult patients with Leber's Hereditary Optic Neuropathy (LHON) is favourable and therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 12 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
In order to further investigate the benefits of Raxone in the treatment of LHON patients, the MAH should conduct and submit the results of an external natural history controlled, open-label intervention study to assess the efficacy and safety of Raxone in the treatment of LHON patients, including long-term treatment.	Interim reports should be provided at the time of annual re-assessments. Due date of final report: 31 August 2020

Description	Due date
In order to further investigate the benefits of Raxone in the treatment of LHON patients, the MAH should maintain and extend the Historical Case Record Survey of Visual Acuity Data from Patients with LHON to serve as the external control to the open label study.	Interim reports should be provided at the time of annual re-assessments. Due date of final report: 31 August 2020
Non-interventional post-authorisation safety study (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. The registry should also be used to generate data on long-term effectiveness.	Reports to be provided at the time of annual re-assessment
The MAH should follow up patients in the existing Expanded Access Programme and submit the final results.	Interim reports should be provided at the time of annual re-assessments. Due date of final report: 31 August 2019

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.