17 January 2013
EMA/191284/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Raxone

International non-proprietary name: IDEBENONE

Procedure No. EMEA/H/C/002425

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

List of abbreviations

AUC	Area under the time versus concentration curve
ASA	Active systemic anaphylaxis
ASMF	Active Substance Master File
ATP	Adenosine triphosphate
C_{max}	Maximum concentration of a drug *in vivo* after dosing.
EC_{50}	Plasma concentration required for obtaining 50% of a maximum effect *in vivo*
et al.	And others
EPAR	European Public Assessment Report
FRDA	Friedreich's ataxia
g	Gram
GLP	Good Laboratory Practice
hERG	Human Ether-A-Go-Go Related Gene
h	Hour
HPLC-MS/MS	High Performance Liquid Chromatography coupled on-line with mass spectrometry
HPLC-UV	High Performance Liquid Chromatography with UV Detector
IC_{50}	The concentration of a drug that is required for 50% inhibition *in vitro*
ip	Intraperitoneal
Idebenone, CV-2619 SNT-MC-17, V10	6-(10-hydroxydecyl)-2,3-dimethoxy-5-1, 4-benzoquinone
L	Litre
LLOQ	Lower limit of quantification
m	Milli
M	Molar
min	Minute
N	Number of observations
n	Nano
PK	Pharmacokinetic
po	Per os
%	Percent
QS-10	6-(9-carboxynonyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone
QS10-C	Conjugates of QS10
QS-8	6-(7-carboxyheptyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone
QS-6	6-(5-carboxypentyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone
QS6-C	Conjugates of QS6
QS-4	6-(3-carboxypropyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone
QS4-C	Conjugates of QS4
QT	Interval measured from the beginning of the QRS to the end of the T wave
QTc	Interval measured from the beginning of the QRS to the end of the T wave, corrected for heart rate
s	Second
t	Time
tid	Three times daily (ter in die)
t_{max}	Time at which C_{max} occurs
µ	Micro

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Santhera Pharmaceuticals (Deutschland) GmbH submitted on 27 May 2011 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 29 September 2010.

The application is submitted in accordance with Article 10(3) of Directive 2001/83/EC. The reference product, Mnesis, 45 mg, tablets, MAH Takeda Italia Farmaceutici SpA, has been granted a Marketing Authorisation in Italy 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: treatment of patients with Leber's Hereditary Optic Neuropathy due to G11778A or G3460A mitochondrial DNA mutations.

Raxone was designated as an orphan medicinal product (EU/3/07/434) on the basis of Article 5 of Regulation (EC) No 141/2000 on 15 February 2007 in the following indication: Treatment of Leber's hereditary optic neuropathy.

The legal basis for this application refers to:

Application pursuant to Article 10(3) of Directive No 2001/83/EC and Article 14(8) of Regulation (EC) No 726/2004.

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

Applicant's request for consideration

Marketing Authorisation under exceptional circumstances

The applicant requested consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of the Regulation (EC) No 726/2004 based on the following claim(s):

- the indications for which the product is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

As there is no authorised orphan medicinal product for a condition related to the proposed indication, Article 8 of Regulation (EC) No. 141/2000 does not apply. Therefore the applicant did not submit a

critical report addressing the possible similarity with authorised orphan medicinal products.

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Mnesis, 45mg, tablets
- Marketing authorisation holder: Takeda Italia Farmaceutici S.p.A
- Date of authorisation: 18 May 1993
- Marketing authorisation granted by:

☐ Member State (EEA) : Italy

- National procedure

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

Scientific advice / Protocol assistance

The applicant received Scientific Advice from the CHMP on 19 November 2009. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

Raxone has been given a Marketing Authorisation in Canada on 28 July 2008.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Concepcion Prieto Yerro

Co-Rapporteur: Kristina Dunder

- The application was received by the EMA on 27 May 2011
- The procedure started on 20 July 2011
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 October 2011 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 7 October 2011
- During the meeting in November 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 November 2011
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 July 2012
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 16 July 2012
- During the CHMP meeting in July 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant

- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 August 2012
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 September 2012
- During a meeting of an Expert group on 9 October 2012, experts were convened to address questions raised by the CHMP
- During the CHMP meeting in October 2012, the CHMP agreed on a second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 9 November 2012
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 29 November 2012
- During the CHMP meeting on 10-13 December 2012, outstanding issues were addressed by the applicant during an oral explanation before the CHMP
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 17 January 2013
- During the meeting on 14-17 January 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion

2. Scientific discussion

2.1. Introduction

Leber's Hereditary Optic Neuropathy (LHON)

Leber's Hereditary Optic Neuropathy (LHON) is the most common of the primary mitochondrial deoxyribonucleic acid (mtDNA) disorders. It is an orphan disease which has a prevalence of approximately 2.2 per 100,000 in the EU (Epidemiological Meta-Analysis, 2011). The great majority of European LHON patients harbour one of three pathogenic mtDNA mutations (G11778A, G3460A and T14484C) which affect complex I (NADH-ubiquinone oxidoreductase) subunits of the mitochondrial respiratory chain resulting in a defect of adenosine triphosphate (ATP) synthesis accompanied by increased production of oxygen free radicals causing retinal ganglion cell dysfunction and apoptosis (Tonska et al., 2010). LHON usually results in an irreversible loss of visual acuity (VA) and blindness.

Current research reveals that while LHON occurs 80% of the time in young men in their twenties, it also occurs in men, and in women, of all ages. In one study the onset of LHON was found to have occurred in men and women as young as six and as old as sixty two. Other research finds that LHON may occur in someone who has no family history of LHON or blindness. Expression of the gene varies with the mitochondrial mutation and the family but in general the chances of the eyes of female carriers remaining healthy are over 85% and of males over 50%.

In the acute phase patients initially experience a painless loss of colour vision followed by a painless decrease in central VA with an enlarging centrocecal scotoma. The disease usually starts in one eye while the second eye usually follows a similar course in a matter of weeks or few months and most patients progress to a bilateral VA of 20/200 or worse within 1 year of disease onset. In the chronic phase, there is usually a fixed bilateral, symmetric visual deficit that is life-long. Fundus changes have

been reported to occur in the pre-symptomatic phase, however, in other cases, the fundus looks entirely normal. With time, the retinal nerve fibre layer (RNFL) degenerates.

Currently, there are no approved treatments to prevent or reverse the loss of vision in LHON.

Idebenone is supposed to mitigate retinal ganglion cell dysfunction in LHON 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.

About the product

Idebenone, the active ingredient in Raxone, is a short-chain benzoquinone antioxidant that has the potential to mitigate retinal ganglion cell dysfunction in LHON by its ability to shuttle electrons onto complex III of the mitochondrial transport chain, thereby bypassing the deficient complex I and allowing production of cellular energy in affected cells.

The oral dosage form Raxone film-coated tablets 150 mg is a conventional tablet formulation manufactured using conventional equipment and procedures at the manufacturing sites of Arena Pharmaceuticals GmbH, Zofingen, Switzerland and Haupt Pharma Wülfing GmbH, Gronau/Leine, Germany. The excipients are of common use in film-coated tablets. The amount of the colorant sunset yellow FCF (E 110), used in the film coat of the tablets, is far below the acceptable daily intake (ADI) given by the European Food Safety Authority.

The proposed indication for Raxone is: *"Raxone is indicated for the treatment of patients with Leber's Hereditary Optic Neuropathy(LHON) presenting for treatment within one year of onset of symptoms".*

The proposed dosing regimen is: *"900 mg/day (administered as 2 film-coated tables three times a day)"*

Mnesis 45 mg tablets is the reference medicinal product which was authorised in Italy in 1993 based on a full stand-alone application. The approved indication is: "*Treatment of cognitive and behavioural deficits due to cerebral pathologies of vascular or degenerative origin*". The regulatory data protection for Mnesis has expired in the Community.

2.2. Quality aspects

2.2.1. Introduction

Raxone is presented as film-coated tablets containing 150 mg of idebenone (the active substance). The tablets are orange, round, biconvex of 10 mm diameter, engraved with the Santhera logo on one side and '150' on the other side.

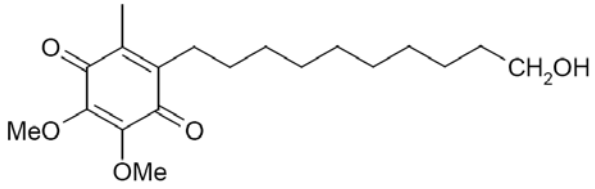
Excipients used in the formulation of Raxone are well known excipients commonly used in tablet formulations, such as lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone K25, magnesium stearate and colloidal silica. These excipients are used to manufacture the tablet cores which are than coated with film-coating consisting of macrogol 3350, polyvinyl alcohol, talc, titanium dioxide (E171) and Sunset Yellow FCF (E110).

The tablets are packed in white high-density polyethylene (HDPE) bottles with white polypropylene (PP) child-resistant tamper-evident twist-off caps.

2.2.2. Active substance

Idebenone, the active substance of Raxone, is well known active substance, chemically designated as 2-(10-hydroxydecyl)-5,6-dimethoxy-3-methyl-2,5-cyclohexadiene-1,4-dione, and has the following structure:

Figure 1. Structural formula of idebenone



It is a yellow-orange, non-hygroscopic, crystalline powder, insoluble in water, freely soluble in ethanol, chloroform, diethyl ether and dioxane and slightly soluble in n-hexane.

Idebenone is a synthetic analogue of ubiquinone, it has no asymmetric atom and is therefore achiral.

The chemical structure of idebenone has been confirmed by means of elemental analysis, infrared spectroscopy (IR), 13C-NMR and 1H-NMR spectroscopy, mass spectrometry (MS) and ultraviolet-visible spectroscopy (UV).

Two polymorphic forms of idebenone are known (form A and B). These forms have different X-ray diffraction patterns and different melting points. Crystallization from solvents leads to form A, whatever the nature of the solvent. Form B is obtained only after melting and re-solidification of form A. The form A is probably the most thermodynamically stable form and this form has constantly been produced with the current process. The substance used for the manufacture of Raxone film-coated tablets is the form A. Polymorphism is not considered an issue as form B has only been formed upon melting and re-solidification of Form A. Furthermore the two forms are distinguishable by their melting point and their IR spectra. Both of these characteristics are controlled at release of the active substance.

Due to poor solubility of idebenone the particle size of the active substance is considered to be a critical parameter for product performance. Therefore the particle size distribution of the active substance is controlled by the specification.

Manufacture

The information on the active substance idebenone is presented in the form of an Active Substance Master File (ASMF).

Idebenone is manufactured through a two-step synthesis followed by crystallisation from two different solvent mixtures. The reagents and solvents are common in chemical synthesis. Conventional chemical reactions are used (catalytic hydrogenation and oxidation). Detailed description of the manufacturing process (including critical steps) has been provided in the restricted part of the ASMF.

Starting materials are well characterised. The description of the manufacturing process, characterisation of the drug substance and impurities are in accordance with the EU guideline on Chemistry of new active substances. The manufacturing process is described in detail and critical steps and controls discussed.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential impurities were well discussed with regards to their origin and characterised. The levels of the impurities with an acceptance criterion higher than max 0.15% were supported by the results of toxicological studies and appropriate specification limits have been set.

Specification

The active substance specification, including parameters, analytical procedures and acceptance criteria was considered suitable for release of batches of the active substance. The specification complies with the requirements of the Q3A (R), Q3C and Q6A ICH guidelines. Justifications have been presented for each of the requirements listed in the specification.

The specification includes tests for appearance and colour (visual examination), appearance of solution, identification (IR, melting point), related substance (HPLC), residual solvents (GC), content of water, sulphated ash, heavy metals, residual catalysts (ICP-AES), assay (HPLC), particle size (laser diffraction) and microbiological purity.

The descriptions of the analytical methods are considered acceptable and their validations are performed in accordance with ICH standards and Ph. Eur. requirements.

Batch analytical data have been provided for nine batches of the active substance. All batches comply with the proposed specifications. Batch analysis results confirm batch to batch consistency and support uniformity of the quality of the active substance.

Stability

Stability data from long term and accelerated stability studies have been provided for three production scale batches from a completed primary study. The batches have been stored in simulated shipping containers. Results were provided from 5 years of storage at 25°C/60% RH and 6 months of storage at 40 °C/75% RH.

In addition, data have been provided from an on-going confirmatory study for three full-scale batches manufactured by the one of the proposed manufacturers and for three smaller batches manufactured by an alternative manufacturer.

The stability program was supplemented by forced degradation studies. The stability against heat and light was studied in solid state. In solution the influence of pH and oxidative conditions were investigated.

Results obtained from the proposed stability program indicate very good stability of idebenone in the solid state. No evidence of instability was observed under long term or accelerated conditions when samples were stored in the proposed container closure system.

The stability data provided support the recommended retest period at the proposed packaging and storage conditions.

2.2.3. Finished medicinal product

Pharmaceutical development

The reference product (Mnesis) was developed as sugar-coated tablets containing 45 mg of the idebenone (the active substance) for the treatment of cognitive disorders.

Idebenone, the active substance of Raxone, has been investigated for the treatment of several orphan diseases, such as Friedreich's Ataxia (FRDA), Leber's Hereditary Optic Neuropathy (LHON), Duchenne Muscular Dystrophy (DMD), Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like Episodes (MELAS) syndrome, and Primary Progressive Multiple Sclerosis (PPMS). Raxone has been developed taking into account that patients suffering from different neuromuscular diseases need a high dosage of idebenone. Coating of the tablet was required due to the intense colour of the active substance. However, sugar coating was excluded because some patients have difficulties swallowing, thus requiring a small tablet. Also a high percentage of Friedreich's Ataxia patients suffer from diabetes mellitus which would have made the use of a sugar coated dosage form difficult for 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.

Tablets of the same qualitative compositions have been used throughout the development.
The excipients have been varied on a quantitative basis to optimize hardness, friability, disintegration and dissolution. The particle size and compression force have been optimized. Provided dissolution profiles demonstrate similar behaviour for the tablets investigated during development.

A rationale has been provided for the use of Sunset Yellow FCF (E110), the azo-dye, in the tablet's coating. The rationale included the difficulties to find a colorant that would be able to mask the spots of orange colour (originating from the intensely orange coloured idebenone) that appear on the tablet surface upon storage. Several colorants as *e.g.* the iron oxides were not an option as the tablets were intended for patients suffering from orphan neuromuscular diseases (Friedreich's Ataxia, Leber's Hereditary Optic Neuropathy (LHON), Duchenne Muscular Dystrophy, MELAS syndrome, and Primary Progressive Multiple Sclerosis). The patients suffering from the Friedrich's Ataxia disease show a modification of their iron metabolism. The use of iron chelators is considered as possible treatment strategy for the Friedreich's Ataxia disease. Therefore, it was intended to avoid any additional intake of iron. Natural colorants were excluded due to insufficient chemical stability. Furthermore, the use of sunset yellow is permitted in medicinal products in accordance with Directive 2009/35/EC on the colouring matters which may be added to medicinal products. The concentration of Sunset Yellow FCF (E110) in the coating of idebenone film-coated tablet is well below the Acceptable Daily Intake (ADI) value.

The development of the product has been satisfactorily performed and explained.

The packaging materials have shown suitability by acceptable product performance characteristics and stability studies.

Adventitious agents

No materials of animal or human origin are used during the manufacture of the active substance.

Lactose monohydrate used in the finished medicinal product is the only material of animal origin used during the manufacture of the product. It is certified by the supplier that the lactose used in this formulation is produced in compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products"

(EMEA/410/01). It is produced from milk obtained from healthy cattle under the same conditions as milk intended for human consumption.

Magnesium stearate is of vegetal origin and relevant certificates from manufacturers of this excipient have been provided.

Manufacture of the product

Raxone film-coated tablets are manufactured using conventional process comprising (1) preparation of granulate by wet granulation, (2) preparation of the compression mixture, (3) compression, (4) preparation of film-coating suspension, (5) coating and (6) packaging.

The manufacturing formula, flow chart and description of the manufacturing process were presented. Critical steps have been identified and appropriate in-process controls were proposed. No intermediates are isolated during manufacture of Raxone film-coated tablets 150 mg.

Process validation data were provided for the manufacturing process performed at one of the two proposed manufacturing sites. Data were provided for three commercial scale batches manufactured at the lower batch scale. Different steps of the manufacturing process were analysed and the data provided confirmed the ability of the process to deliver batches of consistent and sufficient quality. The validation of the manufacturing process has been well documented and satisfactory data provided. Considering the type of manufacturing process (standard process) it was accepted that the formal process validation data at the upper limit of the proposed commercial batch size has not been performed yet.

For the second manufacturing site, a process validation scheme was provided. The validation will be carried out on three consecutive commercial-scale batches prior to marketing of the product. This approach is acceptable considering the type of manufacturing process (standard process) and the standard pharmaceutical form (film-coated tablets) of the product.

Product specification

The product specification includes tests for appearance of tablets (visual), identification of the active substance (HPLC and UV), uniformity of dosage units by mass/weight variation, degradation products (HPLC), dissolution (UV), assay (HPLC) and microbial purity.

A detailed description for all analytical methods was provided. Full method validation data was provided for the non compendial (in-house) analytical methods. The analytical methods have been validated in accordance with ICH guidelines.

Batch analysis data were provided for three batches manufactured at each manufacturing site for the purpose of stability studies. Data were consistent between batches and also between manufacturers. The results comply with the specification and confirm consistency of the product.

Stability of the product

Stability studies have been conducted on three pilot scale batches manufactured by a former manufacturer but from the same process as intended for commercial production and packaged in the proposed container closure system. The stability studies have been carried out according to ICH requirements. Batches of the finished product were stored under the long term conditions (25°C/60% RH) for 48 months and accelerated conditions (40°C/75% RH) for 6 months. In addition

one batch was exposed to light environments according to ICH Q1B. The batches have been tested according to the proposed specification.

Results from long term and accelerated studies revealed no sign of degradation at any of the conditions studied. The light exposure study did not show any degradation.

On the basis of the provided stability data, the assigned shelf life and storage conditions is well supported.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The quality of Raxone has been adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted in support of the marketing authorisation application.

Information on development, manufacture and control of the active substance has been presented in a satisfactory manner. The quality of the active substance is considered sufficiently described and adequately supported by data.

Sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the finished product has been presented. The formulation is considered justified.
The excipients are commonly used in these types of formulations and comply with Ph. Eur. requirements. Their function has been satisfactorily documented. The packaging material is commonly used and well documented.

The manufacturing process of the finished product is a standard process that has been adequately described. The data shows consistent manufacture and is considered sufficient for this manufacturing process.

The proposed specifications were justified based on the batch and stability results, and are in general adequate for assuring the product quality and therefore were accepted.

The results of tests carried out indicate satisfactory 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 the clinic.

The stability program is considered satisfactory. The batches placed on stability are considered representative of the product to be marketed. The results generated during the stability studies support the proposed shelf life and storage conditions.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory manner.

There are no unresolved quality issues, which could have negative impact on the Benefit - Risk balance of the product.

2.3. Non-clinical aspects

2.3.1. Introduction

The MAA for Raxone in the LHON indication is a hybrid application using Mnesis 45 mg idebenone tablets as the reference medicinal product. Therefore, in support of the LHON indication, the applicant presented primary pharmacology data in an animal model of LHON, safety pharmacology studies and nonclinical studies performed with idebenone to support the use of Raxone in LHON. The non-clinical studies sponsored by the applicant were reported to be GLP compliant.

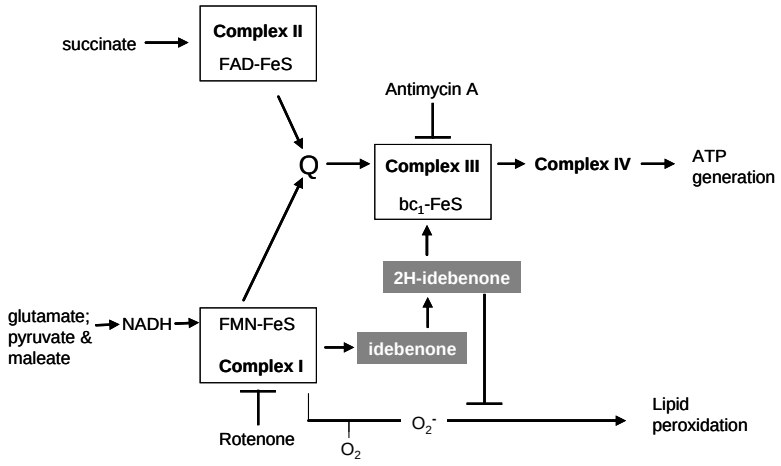
The current document provides an overview of the main findings of the submitted nonclinical studies, nonclinical information with idebenone available in the public domain, and discusses the relevance of these data with respect to the clinical use of Raxone in LHON.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The applicant claims that Idebenone is a synthetic analogue of ubiquinone (coenzyme Q10) and functions as an electron carrier in the mitochondrial electron transport chain, inhibits lipid peroxidation and protects cell membranes and mitochondria from oxidative damage. The proposed mode of action, is that idebenone is reduced by complex I to 2H-idebenone which can return electrons to complex III, thereby facilitating the generation of ATP. The mechanism of action is illustrated below in the figure (based on Sygiyama et al., 1985) (see Figure 1).

Figure 2. Schematic representation of idebenone's proposed mode of action as an electron carrier in the mitochondrial respiratory chain (based on Sugiyama et al. 1985)



FeS: iron sulfur cluster centers. Q: Coenzyme Q; arrows: electron flux.

In vitro and ex vivo data presented suggests that idebenone administration inhibits reactive oxygen species formation and lipid peroxidation restoring ATP levels under conditions of complex I inhibition. In vivo rodent animal models of LHON, shows evidence suggesting that idebenone decreases the pathological changes induced in the retina by complex I inhibition.

The reduced form of the compound Idebenone inhibits lipid peroxidation and swelling of mitochondria. Almost complete inhibition lipid peroxidation was observed at a concentration of 200 µM (EC50 50 µM).

None of Idebenone main metabolites (QS-4, QS-6, QS-10) could prevent lipid peroxidation to the same extent. The inhibition of lipid peroxidation by Idebenone was improved in the presence of the substrates for mitochondrial respiration.

Data from in vitro isolated mitochondria from different animal tissues suggests that idebenone activity effects on cellular electron transfer can help restoring mitochondrial respiration.

In relation with the intended indication, the applicant has carried out a series of in vitro and in vivo studies in mouse model.

Cell culture experiments using the retinal ganglion cell line RGC-5 treated with the mitochondrial complex I inhibitor rotenone showed a significant increase of cell survival up to 58% at concentrations of 1000 nM. An in vivo study using an LHON mice model indicates that idebenone had an effect in the preservation of retinal thickness, and protection from from gliosis. The administered effect dose (200-400mg/kg/day) in the LHON mouse model seems to be below the range of the clinical dosages (15-18 mg/kg/day. Nonetheless when applying conversions for the calculation of the human equivalent dose, the estimates suggest that the concentration that could be reached in the eye is comparable to the concentrations that showed efficacy in vitro and in vivo.

The applicant provides scientific evidence that it is not considered comprehensive enough to prove efficacy for the intended indication based on non-clinical data only, as the models used do not replicate entirely the disease in humans. It is acknowledged that the provided data suggests that the product administration could be helpful for LHON patients nevertheless idebenone's mechanism of action in LHON is not fully elucidated. Efficacy for the requested indication will need to be demonstrated based on clinical data results as the preclinical data is not conclusive.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were conducted by the applicant. The dossier cross-refers this section to the reference product, Mnesis. Since the focus for the application is on the new data relevant for the new proposed indication the CHMP considers that no further secondary pharmacodynamic data is needed.

Safety pharmacology programme

The applicant referred this section to the approved information of the reference product Mnesis.

At the CHMP request the applicant submitted study reports aimed to address the possible effect of idebenone on cardiovascular system (CVS) and QT prolongation. Both in vitro hERG assay and telemetry study in dogs were performed with idebenone at doses higher than the plasma levels observed in the clinical studies. There were no effects on body weights or organ weights, no opthalmoscopic, macroscopic or microscopic changes. A small number of differences were observed in some clinical biochemistry parameters. These were not considered to be of toxicological significance. The toxicokinetic data show that the animals are adequately exposed to idebenone in the studies. In conclusion, no effects on the QTc interval or other cardiological effects were detected in these studies. These results are supported by the clinical findings that show no effect on ECG morphology or the QTc interval in human volunteers or LHON patients receiving idebenone.

Pharmacodynamic drug interactions

The applicant referred this section to the approved information of the reference product Mnesis.

At the CHMP request the Applicant submitted data from studies carried out in order to investigate pharmacodynamic drug interactions of idebenone and the major metabolite Q10. The risk for inhibition of CYP isoenzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) and induction of CYP1A2, CYP2B6 and CYP3A4 is considered to be low.

2.3.3. Pharmacokinetics

In distribution studies performed in rat, after rapid oral absorption was reported. 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. Data shows that a considerable amount of unchanged idebenone was distributed in the mitochondrial fraction (34.4%) was distributed in the mitochondrial fraction. The plasma contained mostly metabolites, with a small amount of unchanged idebenone, which was > 90% protein-bound. Studies performed in pregnant rats shows detecting the product 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 were also excreted into milk in moderate amounts (Torii et al 1985).

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 metabolized and all of the metabolites measured in the plasma or eye fluids were present at higher levels than idebenone in the following order QS4>QS6>QS10>idebenone. The metabolite levels measured in the aqueous humors were much higher than those reported in the vitreous humors (approx. 5 fold). The apparent terminal half-lives (t½) of the product after single oral administration of idebenone, QS10, QS6 and QS4 were 1.70, 2.31, 6.22 and 5.84 hours, respectively.
The absorption/distribution study the eye of in male mice after idebenone administration showed that the ratio (vitreous humor/plasma and aqueous humor/plasma) appeared to be independent of day of dosing thus no accumulation of idebenone and its metabolites in the eye is expected

As soon as Idebenone is absorbed, it is metabolized and drug derived material is rapidly excreted into urine and bile, being eliminated primarily via metabolism. The metabolites were QS-10, QS-8, QS-6 and QS-4 were formed by oxidative shortening of the side chain of idebenone. The parent metabolites were further catabolised by sulfatation and glucuronidation. The metabolic differences among species are more quantitative than qualitative. According to the data available QS-4 was the major plasma metabolite in rats and dogs while QS-10 was predominant in rat bile. In the mouse eye, the levels of three main metabolites (QS-10, QS-6 and QS4) in rat have been analysed. There is no indication that the eye metabolism is different to the tissues studied. As no human specific metabolite has been identified rats and dogs are considered as relevant animal models for toxicity assessment.

Idebenone was eliminated by rats and dogs mostly as metabolites within 48 h. In rats, more was excreted in urine than in faeces, whereas in dogs excretion by these two routes was almost equal. 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. At 72 h after oral or intravenous administration of [14C]idebenone, elimination of radioactivity was complete in rat and dog. In humans, approximately 80% of the dose was found to be excreted via urine.

2.3.4. Toxicology

Mainly published studies have been submitted to characterise the toxicological profile of idebenone. In addition, one 39 weeks chronic toxicity study in dogs, one 4-week repeated toxicity study in rat and two genotoxicity studies performed by the applicant were submitted. To address the carcinogenic properties of idebenone, the applicant referred to the approved reference product Mnesis.

Single dose toxicity

Single dose toxicity was studied in mice and rats after oral, subcutaneous and intraperitoneal administration. The acute toxicity of idebenone was low in both species, where the LD50 was ≥ 10000 mg/kg after oral and subcutaneous administration. After intraperitoneal administration the average LD50 was above 700 mg/kg in mice and above 800 mg/kg in rats. Animals receiving intraperitoneal high doses showed similar toxic signs, including a decreased locomotor activity, hypotonia of the abdominal muscles, loose feces, loss of body weight and emaciation. Mice and rats treated with oral high doses displayed decreased locomotor activity. 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 rat (up to 26 weeks) and dog (up to 12 months). In studies 5 weeks rats and dogs were exposed to idebenone oral doses up to 500 mg/kg/day, although in a rat short study in (2 weeks) animals were dosed up to 2500 mg/kg/day. Coloured urine due to coloured metabolites was observed in both species. Coloured faeces were also seen in dogs occasionally.

The main effect of idebenone in rats was local changes in the forestomach mucosa. Yellow colouration and mucosal thickening of the forestomach, occasionally accompanied by forestom ach dilatation and appearance of red spots in the fore- and glandular stomach was observed at necroscopy. 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. Oedema of the submucosa in the glandular stomach was also noted in rats dosed with 500 mg/kg/day for 26 weeks. From the data collected from these two studies it appears that the target organ was the forestomach, being a rodent-specific organ with low clinical relevance for the human situation. The changes or hyperplasia were observed in the mucosa of glandular stomachs at the mid administered dose of 100 mg/kg and findings in the forestomachs and glandular stomachs were reported in the 500 mg/kg group.

A GLP study in rats carried out with a duration of a month and two week off dose period confirmed the findings reported in the published literature above described where stomach findings were mostly described at 500 mg/kg.

In dogs, no systemic toxicity and no target organ was identified in repeated dose studies carried out with up to one year duration. There were no treatment related effects on body weight or food consumption. The only effects in this species were clinical signs, including gastrointestinal disturbances such as loose faces, diarrhoea and emesis. The erythrocyte count was reduced slightly at 12 months in males receiving 500 mg/kg/day but other erythroid parameters were normal. The biochemical studies also showed occasional significant differences compared with control values, but there was no clear dose relationship. Even though most effects did not display a clear dose effect relationship, the effects reported mainly affected the animals receiving 500 mg/kg body weight/day. Based on this, the NOAEL is considered to be 100 mg/kg body weight/ day.

Genotoxicity

Idebenone has shown no genotoxic potential in in vitro bacterial mutagenicity assays and in in vivo genotoxicity studies including mouse micronucleus assays. Clastogenic potential was reported at high concentrations of idebenone, in the chromosome aberration test. This potential could be considered to be linked to the cytotoxic effect at high concentrations in vitro, which are probably related to the redox properties of the substance.

Carcinogenicity

No formal studies or scientific literature to back the claim of lack of carcinogenic potential of idebenone were submitted. Repeated dose studies literature in rats (up to five weeks) and dogs (up to one year) do not reveal concerns regarding the administration of the product for the duration of the studies. The reference product Mnesis SmPC states that no carcinogenicity concerns are expected from the administration of idebenone.

Reproduction toxicity

A series of literature reported studies were submitted by the applicant along with the reference to Mnesis. The studies included 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 were investigated in male and female rat studies. General toxic effects as hypersalivation and red-brown colouring of the urine, decreased body weight were observed. At 500 mg/kg/day a higher rate of post-implantation losses and lower number of live embryos was reported. There were no other adverse effects at either dose on reproductive performance or on embryogenesis.

In the teratology study in NOAEL was identified as 500 mg/kg/day. One damn dosed 20 mg/kg died but the cause was not attributed to the product. No effect on the development of the foetuses or growth of F1 animals was observed. 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.

In perinatal 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 no different to those identified on repeated dose toxicity studies.

No exposure data from pregnant dams were submitted. In rat, assuming that the exposure is similar for non-pregnant and pregnant animals, the margin of exposure was around 30-fold in the reproductive toxicity studies compared to human exposure for the proposed indication. Submitted studies on reproduction were performed at the recommended doses until maternal toxicity was observed, and in rats adequate exposure margins were shown.

In conclusion according to published data and Mnesis SmPC, idebenone seems to have no effects on fertility and general reproductive performance, and there was no evidence of embryotoxic or teratogenic potential.

Studies in juvenile animals

Taking into account the type of toxicity findings reported in studies that have been carried out with Idebenone, in which no target organs of concern were identified, the two studies conducted in rat and dog and since no differential pharmacokinetics between adults and the paediatric population (>14 years old) are expected, the lack of such studies is considered acceptable.

Impurities

The total of all impurities (identified and unidentified) is set to a maximum of 1.0% and the specification limit for the mayor impurity of Idebenone Impurity A was set to 0.5%. Taking into account that Impurity A was contained at levels up to 0.68% in the qualification studies the impurities level can be considered as qualified.

Local tolerance

The lack of formal local tolerance studies is considered acceptable as the local toxicity findings observed were limited to the forestomach in rats (tissue species specific) and no effects have been reported in dogs.

Photosafety

Idebenone does not absorb light at the wavelengths in the range of 290-700nm. Thus, there is no need for photosafety testing with idebenone.

Dependence

Due to the characteristics and intended use of Idebenone, concerns related to dependence potential are not expected.

2.3.5. Ecotoxicity/environmental risk assessment

The Applicant performed an Environmental Risk Assessment (ERA) for idebenone. The log Pow of idebenone at pH 8.2 is 3.93 therefore screening for persistence, bioaccumulation and toxicity according to regulation (EC) No 1907/2006 is not required since the log Pow of idebenone is below the trigger of 4.5 for a PBT assessment.

Two Fpen values have been calculated: 1.54x10-5 (statistical calculation, considering 2 mutations) and 0.537x10-5 (calculated from all available prevalence data on LHON patients with any mutation, obtained during an information request to European registries, eye hospitals, and other database holders). As the lower of the two values was derived from unverified data sources, the higher value was found acceptable to be used in the calculation of the PECsurfacewater.

The higher refined Fpen value is based on a published epidemiological study: “EPIDEMIOLOGICAL META-ANALYSIS - For Leber’s Hereditary Optic Neuropathy (LHON)” (Mascialino, 2011). The resulting PECs was below action limit of 0.01 µg/L as defined in the ‘Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use’ (EMEA, 2006). Therefore, the CHMP considers that a Phase II (Tier A) environmental fate and effect analysis is not required.

The above calculations do not take into consideration the fact that Raxone is intended to be used in “patients presenting for treatment within one year of onset of symptoms’. The number of patients to be treated in any given year is estimated to be <5% of the overall prevalence given above.

In conclusion, idebenone is not expected to pose a risk to the environment.

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)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}				B/not B
	BCF				B/not B
Persistence	DT50 or ready biodegradability				P/not P
Toxicity	NOEC or CMR				T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0069	µg/L			> 0.01 threshold (N)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or ...	K_{oc} =			List all values
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	species
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	

Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 %CO_2			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/kg	
Sediment dwelling organism		NOEC		mg/kg	species

2.3.6. Discussion on non-clinical aspects

Idebenone is a synthetic analogue of ubiquinone (coenzyme Q10) and functions as an electron carrier in the mitochondrial electron transport chain, inhibits lipid peroxidation and protects cell membranes and mitochondria from oxidative damage. The proposed mode of action is that idebenone is reduced by complex I to 2H-idebenone which can return electrons to complex III, thereby facilitating the generation of ATP.

It is acknowledged that the provided data suggests that the product administration could be helpful for LHON patients nevertheless idebenone's mechanism of action in LHON is not fully elucidated. Efficacy for the requested indication will need to be demonstrated based on clinical data results as the preclinical data is not conclusive.

No effects on the QTc interval or other cardio vascular effects were revealed by the conducted studies.

The drug interaction potential of idebenone is considered low.

No accumulation was reported after repeated dosing in rat, mouse (including the eye) or dog and idebenone were also excreted into milk in moderate amounts

As soon as Idebenone is absorbed, it is metabolized and drug derived material is rapidly excreted into urine and bile, being eliminated primarily via metabolism

The toxicological profile of IDE is characterised in rodents by mucosal thickening and lesions in the gastrointestinal system, mainly in the forestomach, a species-specific organ. In the dog, no stomach pathology was observed and only clinical signs such as loose feces and emesis were evident

Idebenone has shown no genotoxic potential in in vitro bacterial mutagenicity assays and in in vivo genotoxicity studies including mouse micronucleus assays

Idebenone seems to have no effects on fertility and general reproductive performance, and there was no evidence of embryotoxic or teratogenic potential

Studies conducted by the applicant support the qualification of the main impurity in Raxone: Impurity A.

Idebenone is not expected to pose a risk to the environment.

Even though most of the non-clinical information was cross-refered to Mnesis, the conducted studies were considered appropriate and sufficient together with the scientific literature provided for the assessment of this application. Where information was deemed insufficient further clarifications and /or additional data has been requested. The applicant has presented satisfactory clarifications regarding safety pharmacology (CVS and QT prolongation) and pharmacodynamic drug interaction and no further non-clinical information was deemed necessary.

2.3.7. Conclusion on the non-clinical aspects

The provided data suggests that the product administration could be helpful for LHON patients nevertheless idebenone's mechanism of action in LHON is not fully elucidated. Efficacy for the requested indication will need to be demonstrated based on clinical data results as the preclinical data is not conclusive.

Non-clinical data reveal no safety concern for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.4. Clinical aspects

2.4.1. Introduction

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**

Type of Study	Study Identifier	Objectives of the Study	StudyDesign 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, parallelgroup, 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, parallelgroup, randomised, single and repeated t.i.d dose	Idebenone Group A:1x150 mg t.i.d. Group B: 5 x 150 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 Leber's Hereditary Optic Neuropathy	6 months
Clinical Efficacy and Safety	SNT-II-003-OFU (RHODOS - follow up)	To assess the current logarithm of the minimum angle of resolution (logMAR) visual acuity of LHON patients who participated in the SNT-II-003 trial and compare this to their logMAR visual acuity at Visit 2/Baseline and Visit 5/Week 24 or last treatment visit of SNT-II-003 (RHODOS)	A single visit, observational follow-up study of patients participating in SNT-II-003	No treatment	Completed 60 patients (idebenone 41/placebo 19)	Patients with Leber's Hereditary Optic Neuropathy	NAP

2.4.2. Pharmacokinetics

Absorption

Pharmacokinetic data on idebenone have been obtained from 4 clinical pharmacology studies (SNT-I-001, SNT-I-002, SNT-I-003 and SNT-I-004).

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.

Pharmacokinetic parameters were calculated by using non-compartmental methods. Standard statistical methods were applied.

Absolute bioavailability of idebenone has not been studied given that it has not been administered IV.

After administration in fasting conditions, t_{max} of unconjugated and total idebenone is reached with a median (range) of approximately 0.67 (0.33-5) hours and 1.33 (0.67-2.67) hours respectively. The corresponding figures in high-fat conditions are 1.17 (0.67-3.50) and 1.33 (1.00-3.00) hours.

Data provided indicate that food modifies the bioavailability of idebenone. In fact, the increase in Cmax is around five-fold when the drug is administered with food. AUC also increases (6-fold) when idebenone was given in fed conditions. When only one dose of idebenone is administered plasma concentrations are below the limit of quantification.

Distribution

No data on distribution in humans has been submitted however the applicant bridges this section to Mnesis, approach that is considered acceptable.

In vitro and animal studies literature data has been submitted. In distribution studies performed in rat, rapid oral absorption was reported. 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. Data shows that a considerable amount of unchanged idebenone was distributed in the mitochondrial fraction (34.4%) The plasma contained mostly metabolites, with a small amount of unchanged CV-2619, which was > 90% protein-bound.

Elimination

Unconjugated idebenone is metabolised to phase-I metabolites (QS10, QS8, QS6 and QS4) via unknown CYP enzymes which catalyses shortening of the carbon side chain. Further phase II metabolites are formed from the action of glucuronidases and sulfatases, likely in parallel to the oxidative metabolism. The metabolites of idebenone (Q4 and Q6) are conjugated and excreted, predominantly by the kidney. Non-clinical investigations show that metabolites are inactive or have very little activity. However, less than 1% of idebenone and its metabolite Q10 are excreted by the kidneys.

No true clearance values were available since no intravenous formulation was administered. The mean terminal half-life after a single dose was approximately 10 hours, ≈5 hours, ≈6 hours and 6 hours after single oral administration for total idebenone, total QS10, total QS6 and total QS4 respectively. No terminal half-life of unconjugated idebenone could be determined with the sampling schedule applied.

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. For unconjugated idebenone, the data does not allow any assessment of time dependency since AUC∞ is not determined after a single dose.

The consequences of possible genetic polymorphism have not been evaluated.

Limited information on pharmacokinetics is available in the target population. Results from the plasma sampling analysed show levels that seem lower for patients included in RHODOS study than those seen

in studies in Friedrich's Ataxia. This is expected given that the dose administered to patients with Leber's disease was lower.

Special populations

Regarding PK in special populations, the Applicant did not submit data for renal and hepatic impaired subjects, however the applicant has developed a Population PK model in which age, race, body mass index, body weight, health status, food effect, creatinine clearance, transaminases, bilirubin and disease severity were incorporated as covariates. Food and body weight were considered as relevant factors although the latter seems to represent a small percentage of the large variability of the product therefore it is agreed that no dose adjustment based on weight is recommended.

The administration of idebenone for a long period of time (i.e. > 3years) and as consequence the chronic treatment of LHON patients until reaching advanced age is unlikely. Although unexpected, LHON may occur in the elderly and therefore, Raxone may happen to be administered to elderly patients. In view of the usually low age of onset of LHON (18 to 30 years of age), the rarity of LHON in patients above 60 years of age and the relatively short duration of therapy (Stabilization is expected to be achieved within 3 years of the initiation of therapy) and considering that factors such as age, BMI or renal function do not appears to significantly affect PK parameters it is agreed that no specific dose adjustment is warranted in elderly population.

Raxone has not been studied in children under 14 years. However, the applicant has presented safety data in subjects with Friedreich's Ataxia (FRDA) as young as 8 years of age, at weight adjusted doses of up to 2250 mg/day (a level higher than the recommended unadjusted dose of 900 mg/day in LHON), where no safety issues were detected.

Pharmacokinetic interaction studies

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

Pharmacokinetics using human biomaterials

The applicant has submitted in vitro studies on the inhibition by idebenone/QS10 of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 and induction of CYP1A2, 2B6 and 3A4 using human liver microsomes. Inhibition constants (Ki:s) were determined by testing different types of inhibition. Based on the obtained results, no relevant systemic inhibition/induction of the tested CYP enzymes is likely. However, intestinal inhibition of CYP3A4 cannot be excluded therefore additional data collected in an in vivo interaction study with oral midazolam should be provided in order to address this issue.

An in vitro study evaluating the potential of idebenone being a p-gp substrate and inhibitor was submitted. When idebenone was evaluated as substrate of p-gp, low recovery was observed at the three lowest concentrations. The efflux ratio was evaluated in an additional experiment at a lower concentration performed with albumin in order to improve recovery. It showed that idebenone is unlikely to be a relevant p-gp substrate.

Based on the intestinal exposure and with possible 7-fold higher concentrations than the IC50s, inhibition of p-gp cannot be ruled out. The interaction potential of other medicinal products effect on idebenone/QS10 has not been fully elucidated. The relative contribution of direct glucuronidation versus oxidative metabolism has not been sufficiently clarified to conclude that the interaction potential of other medicinal products is low. It has also not been shown which CYP enzyme is primarily responsible for the oxidative reactions associated with the metabolism of idebenone/QS10.

2.4.3. Pharmacodynamics

Mechanism of action

Primary and Secondary pharmacology

No pharmacodynamic studies have been performed by the applicant in LHON patients.

An in vivo study using a LHON mice model indicates that idebenone has an effect on the preservation of retinal thickness and protection from gliosis. The animal model used does not totally replicate the disease in humans although it suggests that idebenone could be helpful for LHON patient. Cell culture experiments using the retinal ganglion cell line RGC-5 treated with the mitochondrial complex I inhibitor rotenone showed a significant increase of cell survival up to 58% at concentrations of 1000 nM. When applying conversions for the calculation of the human equivalent dose, the estimates suggest that the concentration that could be reached in the eye is comparable to the concentrations that showed efficacy in vitro.

Further confirmation on the effect of idebenone in LHON has to be based on the results of the pivotal safety and efficacy trial submitted with this application.

2.4.4. Discussion on clinical pharmacology

Data provided indicate that food modifies the bioavailability of idebenone. In fact, the increase in Cmax is around five-fold when the drug is administered with food. AUC also increases (6-fold) when idebenone was given in fed conditions. These findings indicate that Raxone should be administered with food.

No data on distribution in humans has been submitted however the applicant bridges this section to Mnesis approach that is considered acceptable. As per Mnesis' SmPC, idebenone passes the blood-brain barrier and is distributed at significant concentrations in cerebral tissue.

The metabolism and elimination is not fully investigated, although it can be concluded that the major route of elimination is liver and/or presystemic metabolism (possibly gut metabolism) and that the majority of the dose is excreted in urine as conjugated metabolites.

There are no studies submitted in special populations therefore caution is advised in treatment of hepatic or renal impaired patients.

No specific dose adjustments are warranted for elderly population.

Raxone has not been studied in children under 14 years.. Given that LHON may occur also during the childhood, safety data in children under 14 should be considered as missing information and to be collected during the proposed product registry study.

Interaction studies in vivo are lacking.

In vitro inhibition and induction studies have been conducted, showing no significant inhibition on CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4 or induction on 1A2, 2B6 and 3A4 by idebenone and QS10. Inhibition of intestinal CYP3A4 should be investigated in an in vivo interaction study with oral midazolam. The effect of other medicinal products on idebenone/QS10 is still considered as missing information.

Although the mechanism of action of idebenone is non-specific, the retina is a tissue with extreme energy requirement and the support for an antioxidative action/inhibition of lipid peroxiadation of idebenone is derived from published in vitro and preclinical in vivo studies. Potential secondary

pharmacological effects have not been addressed, but in view of the antioxidative nature of idebenone, no additional data are required.

There is no information on pharmacodynamic drug-drug interactions, however, since LHON patients generally not are prescribed any specific concomitant medication (with the exclusion of vitamins), no additional data are requested.

Due to the general antioxidative effect of idebenone, no differences would be expected for the three primary mtDNA mutations in LHON (G11778A, G3460A and T14484C).

2.4.5. Conclusions on clinical pharmacology

The interaction potential of idebenone and QS10 on other medicinal products is considered adequately investigated with the exception of investigation of pre-systemic interaction (effect on substrates with intestinal CYP3A4 metabolism).

2.5. Clinical efficacy

2.5.1. Dose response studies

No formal dose-response studies have been performed by the Applicant. Data on animals suggest that, in theory, 300 mg TID may give aqueous humour levels in the range where idebenone prevented ganglion cell death in the preclinical models (see Non-Clinical and Clinical Assessment report).
The choice of the dose (900 mg/day) was based on previous studies in patients with Friedreich's ataxia (FRDA) where no additional benefit of 2250 mg/day over 900 mg/day was shown. This posology is also within the range of doses administered to LHON patients in published studies of reference.

Although the difficulties to perform a dose-finding study in such a rare disease are acknowledged, it cannot be concluded that the dose selected is the one with the best ratio between efficacy and safety due to lack of data.

2.5.2. Main study

The RHODOS study constitutes the main basis to support the efficacy and safety of idebenone in the treatment of LHON patients. The aim of the study was to assess whether administration of idebenone can improve visual function in these patients. It was initially conceived as an exploratory trial to be subsequently validated in a larger confirmatory trial. Due to the difficulties in recruiting patients with this condition and after consultation with the Scientific Advice Working Party and national agencies the study was amended to be used as a “pivotal” trial supportive of the marketing authorisation of the product.

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 (RHODOS) Study Number: SNT-II-003

Methods

Study Participants

The study was a double-blind, randomized, placebo-controlled, parallel group study where up to 84 patients were to be randomized to receive either idebenone or placebo in a ratio of 2:1. The dose of idebenone was 900 mg/day. Patients were treated as out-patients. Their participation in the study lasted approximately 32 weeks: up to 4 weeks for the screening phase, 24 weeks for the treatment phase and a 4-week follow-up phase.

This was a 3-center study conducted in Germany (Munich), United Kingdom (Newcastle-upon-Tyne), and Canada (Montreal).

- **Inclusion Criteria**

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

1.Age ≥14 years and < 65 years

2.Impaired visual acuity in at least one eye due to LHON

3.Onset of visual loss due to LHON was five 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).

9.3.2

- **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 hematology 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

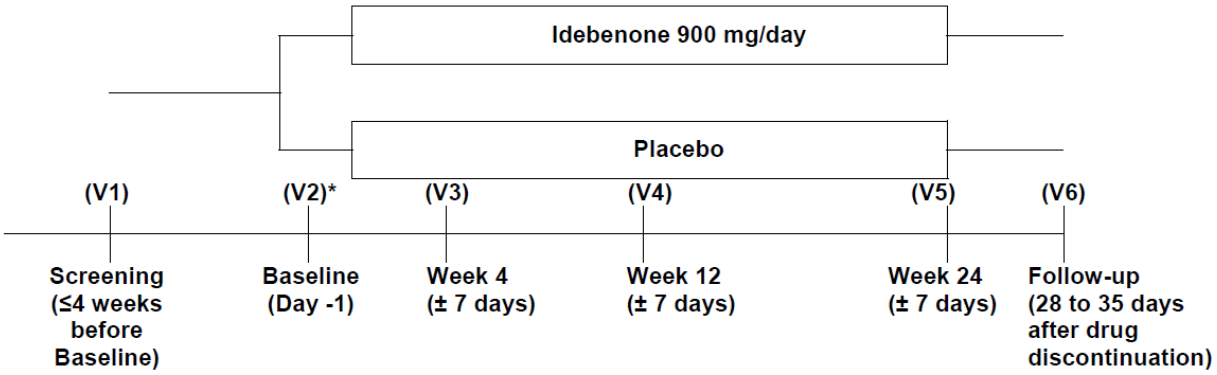
6.Participation in another clinical trial of any investigational drug within 3 months prior to Baseline

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

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.(see figure3 below)

Figure3. Study design



*Subjects were randomized at Visit 2 and took the first dose of study medication on the morning of the day after Visit 2 (Day 1).
V = Visit

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 color 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

- **Primary endpoint**

- Best recovery of logMAR visual acuity between Baseline and Week 24 in either right or left eye

- **Main secondary endpoint**

- Best visual acuity at Week 24 (best eye at Week 24) compared to best visual acuity at Baseline (best eye at Baseline)

- **Other secondary endpoints**

- Count of eyes/patients for which the visual acuity improves between Baseline and Week 24
- Change in visual acuity between Baseline and Week 24 of the patient's best eye at Baseline
- LogMAR visual acuity 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 visual acuity 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 color contrast sensitivity as a continuous variable in both eyes (in a subset of patients)
- logMAR visual acuity as a continuous variable in both eyes
- Clinical Global Impression of Change
- Change in HRQOL assessed by VF-14 questionnaire
- Change in self-reported general energy levels assessed by VAS
- Plasma levels of idebenone matched to measures of efficacy and safety.

Sample size

The sample size of 84 patients for this study was estimated based on the following assumptions for patients in the ITT population: visual acuity 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 visual acuity 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).

Randomization was stratified by disease history (factor with two levels: onset more or onset less than one year prior to randomization) and by mutation type (three levels: G11778A, G3460A and T14484C), to ensure balanced treatment allocation within the six resulting strata.

The randomization procedure was centralized (BIOP AG, Basel, Switzerland). For each of the six strata a computer-generated randomization list was created (Clintrak, Allschwil, Switzerland) with blocks

containing idebenone and placebo allocations in the correct proportion but in random order. The block size was 6.

Blinding

The treatment allocation was double-blinded. 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. The sites, the sponsor, the DSMB and any contract research organization (CRO) involved in the study conduct were provided with code break cards. Each card was labeled with the patient/medication kit number and the treatment identification (idebenone or placebo) was hidden under a seal.

Unblinding of a patient's treatment, i.e., any of the persons mentioned above de-coding the treatment allocation during the course of the study by removing the seal on the code break card, 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

Analysis Populations

Three populations were defined for this study: the safety population, the Intent-to Treat (ITT) population, and the Per Protocol (PP) population.

- **Safety Population**

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

- **ITT population**

Analyses of all efficacy variables were performed on the ITT population. This population included all randomized patients who received at least one dose of the study medication. Patients were analyzed as randomized regardless of protocol violations. For visual acuity endpoints, three randomized and treated patients were prospectively excluded from the ITT population due to inaccurate recordings in visual acuity measurements either at Baseline or at Visit 5 (Week 24) (refer to Appendix 16.1.9, SAP, Appendix 1).

- **PP population**

Selected efficacy variables, including the primary efficacy variable, were assessed in the PP population, in addition to the ITT population, as described in the following sections. 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.

Handling of missing data

For all continuous efficacy variables in the ITT and PP populations (visual acuity, visual fields, optic nerve fibre layer thickness, color contrast sensitivity, health-related quality of life (VF-14) questionnaire, energy level by visual analog scale,) the following methods was used to impute missing data:

- **Primary method for handling missing data:**Mixed-Model Repeated Measures (MMRM): In contrast to other imputation methods, in which the analyses are applied to the observed and

imputed data, MMRM utilizes only the observed data. It makes inferences based on the multivariate normal distribution, with parameters estimated from the available data. The inferences are valid assuming the missing data are “missing at random”, meaning that data are missing randomly conditional on the available values and the factors in the model; in particular, whether a data point is missing is independent of its actual (unknown) value. (Note: this approach requires the application of certain statistical models, including visit and visit*treatment interaction).

- **Imputation method 1:** Missing values are imputed with a mean of the available post-baseline visits (i.e. from Visit 3 (Week 4), Visit 4 (Week 12) or Visit 5 (Week 24)).
- **Imputation method 2:** Missing data are imputed with the last available observation carried forward (LOCF). The last available measurement which was done not later than one day after the last day of study drug intake will be used as the observation to be carried forward.
- **Observed cases (OC):** An analysis will be conducted based on the available data with no imputation of missing data.

For all categorical efficacy variables in the ITT and PP populations the following methods will be used to impute missing data:

- **Imputation method 1:** Missing data are imputed with the last available observation carried forward (LOCF). The last available measurement which was done not later than one day after the last day of study drug intake will be used as the observation to be carried forward.
- **Imputation method 2:** Patients who have missing data due to discontinuations are treated as “failed” in case of a categorical responder analysis for VA. For categorical analyses of CGIC, HRQOL, patient’s general level of fatigue and self-reported general energy levels such “failure” will result in allocating this patient to the worst possible category.

In addition, exploratory sensitivity analyses are being performed only for the primary and main secondary end point using the following data imputation methods:

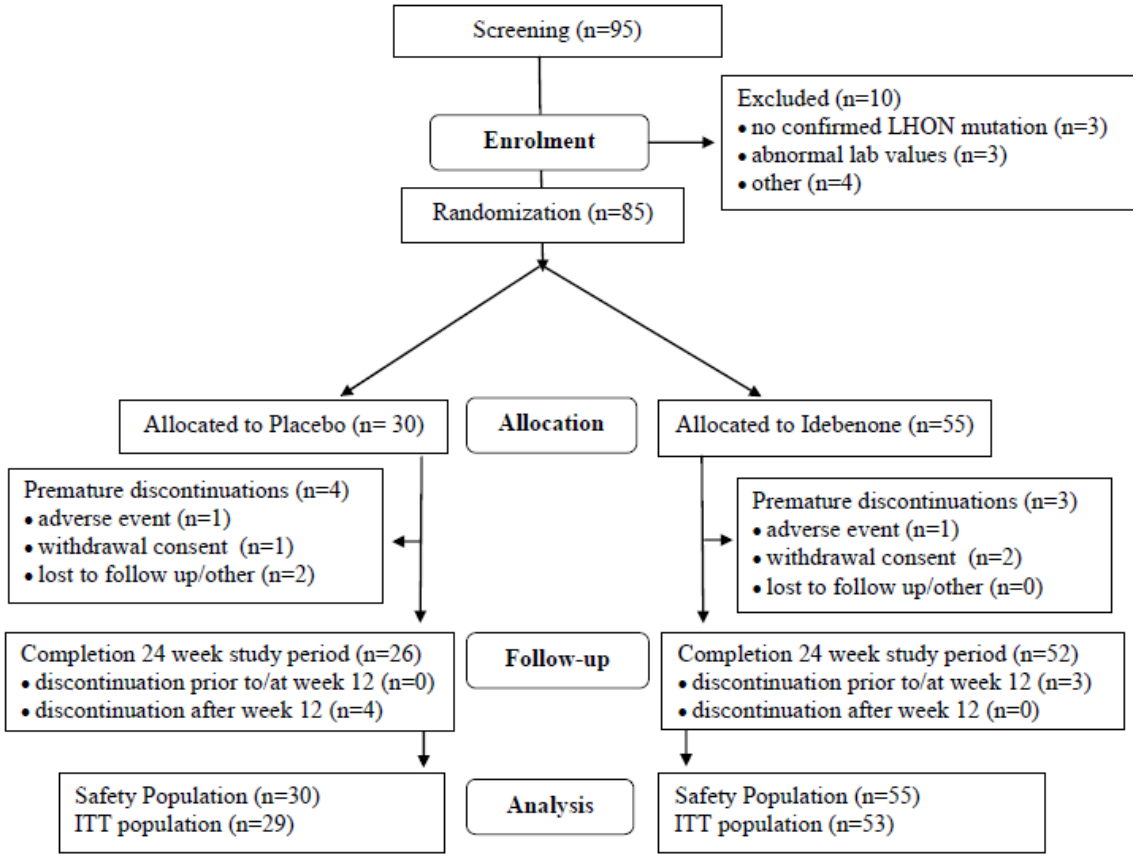
- **Best case scenario:** The best available efficacy variable from any post-Baseline visit (i.e. Visit 3 (Week 4), Visit 4 (Week 12) or Visit 5 (Week 24)) will be used to impute missing data
- **Worst case scenario:** The worst available efficacy variable from any post-Baseline visit (i.e. Visit 3 (Week 4), Visit 4 (Week 12) or Visit 5 (Week 24)) will be used to impute missing data

The assessments which were done more than one day after the last day of study drug intake will be excluded from the efficacy analyses.

Missing safety data (e.g. laboratory tests, vital signs, physical examination) will not be imputed.

Results

Participant flow



Recruitment and conduct of the study

- **Screened and randomized patients**

Ninety-five patients were screened for the study and details of the reasons for excluding 10 patients from randomization are provided in table 2.

Table 2. Screening Failures

NUMBER OF SCREENING FAILURES	10
REASON	
(MISSING)	1
GGT = 205 (OVER RANGE)	1
HAS NO LHON	1
ONSET OF VISUAL LOSS MORE THAN 3 MONTHS AND VISION IN LEAST AFFECTED EYE IS WORSE THAN LOG MAR 0.4	1
PATIENT UNWILLING TO STOP TAKING IDEBENONE - SCREEN FAILURE	1
AST = 66 (OVER RANGE)	1
CLINICAL HAEMATOLOGY	1
LOGMAR DOESNT FIT TO THE INCLUSION CRITERIA	1
NO COFIRMATION OF LHON	1
NO CONFIRMATION OF LHON	1

A total of 85 patients were randomized to study treatment, 55 to idebenone 900 mg/day and 30 to placebo. All 85 randomized patients were included in the Safety Populations. Three patients (two treated with idebenone and one treated with placebo) were prospectively excluded from the ITT population, due to inaccurate recordings in visual acuity measurements, for the analysis of visual

acuity endpoints and thus 53 patients treated with idebenone and 29 patients treated with placebo were included in the ITT population for all visual acuity endpoints. All 85 subjects with available data were included in other ITT analyses. The PP population included 65 patients, 41 treated with idebenone and 24 treated with placebo.

- **Premature Discontinuations**

Of the 85 patients randomized and treated, 7 patients discontinued the study prematurely, 3 patients (5.5%) treated with idebenone and 4 patients (13.3%) treated with placebo. The reasons for premature discontinuation are summarized in Table 3. 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 (patient 070 in the idebenone group and patient 092 in the placebo group).

Table 3. Patient Disposition: Premature Discontinuations (ITT Population)

	Idebenone N=55 n (%)	Placebo N=30 n (%)	Total N=85 n (%)
Total discontinued	**3 (5.5)**	**4 (13.3)**	**7 (8.2)**
Adverse event	1 (1.8)	1 (3.3)	2 (2.4)
Patient withdrew consent	2 (3.6)	1 (3.3)	3 (3.5)
Lost to follow up	0	1 (3.3)	1 (1.2)
Other	0	1 (3.3)	1 (1.2)

- **Protocol Violations / Deviations**

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.

Three randomized patients (patients 005, 013 and 020) with major protocol deviations (reason for major deviation: visual acuity test was not performed according to protocol) were also excluded from the ITT population for all visual acuity analyses due to inaccurate recordings in visual acuity measurements either at Baseline or at Visit 5 (Week 24). For sensitivity analyses, the data for these patients were to be included in exploratory data analyses.

- **Protocol Development and Amendments**

Since LHON generally presents initially in one or both eyes, but with both eyes usually affected by between 4 and 12 months of visual loss in the first eye, it was decided that prevention of visual loss in the initially least affected eye presented an appropriate objective for the study. The primary objective was therefore “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 visual acuity 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 randomized 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 an attempt to improve recruitment by widening the potential patient pool and easing the rigorous inclusion and exclusion criteria. 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 <1> year was introduced) and the exclusion of patients with visual acuity in their least affected eye worse than 0.4 logMAR was correspondingly eliminated. 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 recognized in Amendment 3 that the new best recovery of visual acuity primary endpoint would not necessarily reflect changes in visual acuity relevant to the patient's overall ability to see. Therefore, change in the patient's best logMAR visual acuity between Baseline and Week 24 (where the patient's visual acuity in the better seeing eye at Baseline would be compared to the patient's visual acuity 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.

The study duration was also shortened from 36 weeks to 24 weeks and the patient randomization ratio changed from 1:1 to 2:1 in favor of idebenone, in an attempt to encourage patients to enrol.

Following these amendments, it became possible to identify eligible patients from existing registries and to randomize these patients into the trial, albeit at an extremely slow rate.

The rationale for the introduction of the new secondary endpoint of: best visual acuity at Week 24 versus best visual acuity at Baseline was presented in Amendment 3 and described above. This endpoint was discussed with the CHMP (EMEA/CHMP/SAWP/71341/2009), who supported its introduction.

Baseline data

- **Demographics**

In the safety and ITT populations, idebenone and placebo treatment groups were well-matched for demographic characteristics. The mean age of patients recruited was 33.7 years and the majority of patients recruited were male (73 patients [85.9%]). Almost all patients (83 patients [97.6%]) were Caucasian/white. A summary of demographic characteristics is presented in Table 4.

Table 4. 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)

- **Smoking History**

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. As shown in Table 5, the smoker pack year history was slightly higher for the placebo group than for the idebenone group.

Table 5. Smoking History (ITT Population)

	Idebenone N=55	Placebo N=30	Total N=85
Current smokers, n (%)	21 (38.2)	13 (43.3)	34 (40.0)
Current or former smokers, n (%)	33 (60.0)	18 (60.0)	51 (60.0)
Time abstinent for former smokers, years			
Mean (SD)	4.08 (6.583)	5.30 (8.906)	4.46 (7.098)
Median (range)	1.25 (0.2 – 22.0)	0.50 (0.5 – 21.0)	1.13 (0.2 – 22.0)
Smoker Pack Years			
Mean (SD)	11.18 (11.624)	18.21 (23.128)	13.81 (16.991)
Median (range)	5.50 (0.3 – 47.0)	12.75 (0.2 – 100.0)	9.00 (0.2 – 100.0)

- **History of LHON and Baseline Visual Acuity**

For the safety population the history of LHON was similar in the two treatment groups. The mean (SD) time since onset of visual loss was 22.8 (16.20) months for the idebenone group and 23.7 (16.42) months for the placebo group. The proportion of patients with onset of symptoms less than one year previously was similar in the two treatment groups being 19 patients (34.5%) in the idebenone group and 11 patients (36.7%) in the placebo group.

A summary of the mtDNA mutations at baseline is shown in Table 6 for the safety and ITT populations.

Table 6. mtDNA Mutations (ITT Population)

	Idebenone N=55 n (%)	Placebo N=30 n (%)	Total N=85 n (%)
mtDNA mutation at baseline			
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)

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. Details of the onset of symptoms are summarized in Table 7 for the safety population.

Table 7. History of LHON (ITT Population)

	Idebenone N=55	Placebo N=30	Total N=85
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)
Onset of symptoms >1 year previously, n (%)	36 (65.5%)	19 (63.3%)	55 (64.7%)

Numbers analysed

Three populations were defined for analysis purposes: safety population, ITT population and PP population.

- The safety population included all randomized patients and was used for all safety analyses. This population included 85 patients, 55 treated with idebenone and 30 treated with placebo.
- The ITT population included all randomized subjects who received at least one dose of randomized study medication (85 patients). However, 3 randomized and treated patients were prospectively excluded from the ITT population for all visual acuity analyses (see Section 10.2) and thus the ITT population for this variable included 82 patients, 53 treated with idebenone (96.4% of those randomized) and 29 treated with placebo (96.7% of those randomized). The ITT population was the primary population for efficacy analyses.
- The PP population was a subset of the ITT population and included all data from subjects in the ITT population who had no major protocol deviations (described in Section 10.2). In addition, one patient (patient 67) was recorded erroneously as a non-completer in the CRF and so 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 randomized) and 24 treated with placebo (80.0% of those randomized). Selected efficacy variables, including the primary efficacy variable, were assessed in the PP population, in addition to the ITT population.

Outcomes and estimation

- **Primary end-point**

The primary endpoint (*best recovery of logMAR VA in either right or left eye at 24 weeks of treatment*) did not reach statistically significant difference in VA between treatment arms although the result was numerically better for patients on idebenone (mean difference equivalent to 3 letters; p=0.291) (see Table 8).

Table8. Primary Endpoint: Best Recovery in Visual Acuity (ITT Population)

Change Baseline to	Estimated Change[1] (95% CI) [estimated change in letters]		Estimated Difference[1] ± SEM (95% CI) [difference in letters]	p-value
	Idebenone	Placebo	Idebenone vs. Placebo	
N	53	29		
Week 4	-0.070 (-0.150, 0.010) [+3 letters]	-0.028 (-0.130, 0.075) [+1 letter]	-0.042 ± 0.059 (-0.159, 0.075) [2 letters]	0.478
Week 12	-0.085 (-0.165, -0.004) [+4 letters]	-0.038 (-0.141, 0.064) [+1 letter]	-0.046 ± 0.060 (-0.164, 0.072) [2 letters]	0.439
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
[2]Week 4-24	-0.097 (-0.169, -0.025) [+4 letters]	-0.046 (-0.137, 0.045) [+2 letters]	-0.051 ± 0.051 (-0.152, 0.051) [2 letters]	0.321

Results for the PP population were consistent with those seen for the ITT population. This trend in favour of idebenone was consistently observed in the sensitivity analyses carried out, when different imputations were considered.

- **Secondary end points**

Regarding secondary endpoints, the difference between both treatment arms in Best VA at week 24 was larger (6 letters; p=0.078) although still not statistically significant. Better results were observed in the subgroup analysis where the effect size was larger and statistically significant in patients with G11778A and G3460 mutations and low chance of spontaneous recovery (difference of 8 letter, p=0.037) what suggest that these subgroups could experience some improvement. As expected, there was a high degree of spontaneous recovery in the subgroup with the T14484C mutation what explains the lack of effect of idebenone over placebo. (see table 9)

Table 9. Main Secondary Endpoint: Best Visual Acuity

Change Baseline to	Estimated Change[1] (95% CI) [estimated change in letters]		Estimated Difference[1] ± SEM (95% CI) [difference in letters]	p-value
	SAN Idebenone	Placebo	SAN Idebenone vs. Placebo	
ITT Population (SAN Idebenone n=53, placebo n=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
Mutations G11778A and G3460A (SAN Idebenone n=42, placebo n=23)				
Week 24	-0.034 (-0.145, 0.077) [+1 letter]	0.134 (-0.008, 0.276) [-6 letters]	-0.169±0.080 (-0.326, -0.011) [8 letters]	0.037

A number of pre-specified responder analyses were carried out in order to assess the clinical relevance of idebenone.

When response was defined as the lack of a significant deterioration (scoring logMAR 1.0) a significant response was achieved by patients with preserved vision (logMAR ≤ 0.5 at baseline).

When response was defined as improvement of visual acuity (change of at least logMAR 0.2) idebenone performed (9% to 13%) better than placebo in LHON patients. Whether this improvement means a true benefit is uncertain although it confirms the positive tendency when the results are translated into a more intuitive measure for patients. (see Table 10)

Table 10. Selected other VA Endpoints week 24: Assignment of logMAR 2.0, 2.3 and 2.6 for CF, HM and LP, respectively. ITT population.

	Idebenone	**Placebo**	**Idebenone vs. Placebo**	
N	N=53	N=29	Estimated difference (95% CI) [letters]	p
Proportion in whom VA in the initially least affected eye does not deteriorate to ≥logMAR 1.0 (patients with an eye ≤0.5 logMAR) (missing value=deterioration, Tab 14.2-3.1)				
N baseline	6	2		
N Week 24	0	2		0.036
Best recovery: Proportion of patients improved ≥ 0.2 logMAR (missing value = no improvement, Tab 14.4.7.1)				
N	N=53	N=29		
Week 24	20/53 (37.7%)	7/29 (24.1%)		0.231
Best visual acuity: Proportion of patients improved ≥ 0.2 logMAR (missing value = no improvement, Tab 14.4.7.2)				
Week 24	14/53 (26.4%)	5/29 (17.2%)		0.420

There was a statistically significant difference in favour to placebo in the proportion of patients in whom the VA in the initially least affected eye does not deteriorate to logMAR 1.0 or more (in patients with an eye ≤0.5 logMAR). None of patients in the idebenone group showed deterioration to logMAR 1.0 or more whereas the two patients on placebo showed such deterioration.

For the primary and key secondary endpoint, subgroups were analysed by disease duration (>1 year, < 1 year), age (< 30 years, > 30 years) and smoking status (Y/N). Independent on disease duration, a numerical favour was observed for idebenone (key secondary endpoint >1 year: 3 letters, p=0.0332, < 1 year: 10 letters, p=0.190). For the key secondary endpoint, subjects over 30 years of age appeared to have no effect of the active treatment (0 letters difference between treatment arms, p=0.998), while an 11 letter difference in favour of idebenone (p=0.025) was observed in younger subjects. While no benefit of idebenone was observed in smokers, the effect was fairly convincing in non-smokers (key secondary endpoint smokers: 2 letters, p=0.665, non-smokers: 9 letters, p=0.025). The effect in the non-smoker subgroup was primarily driven by the placebo group.

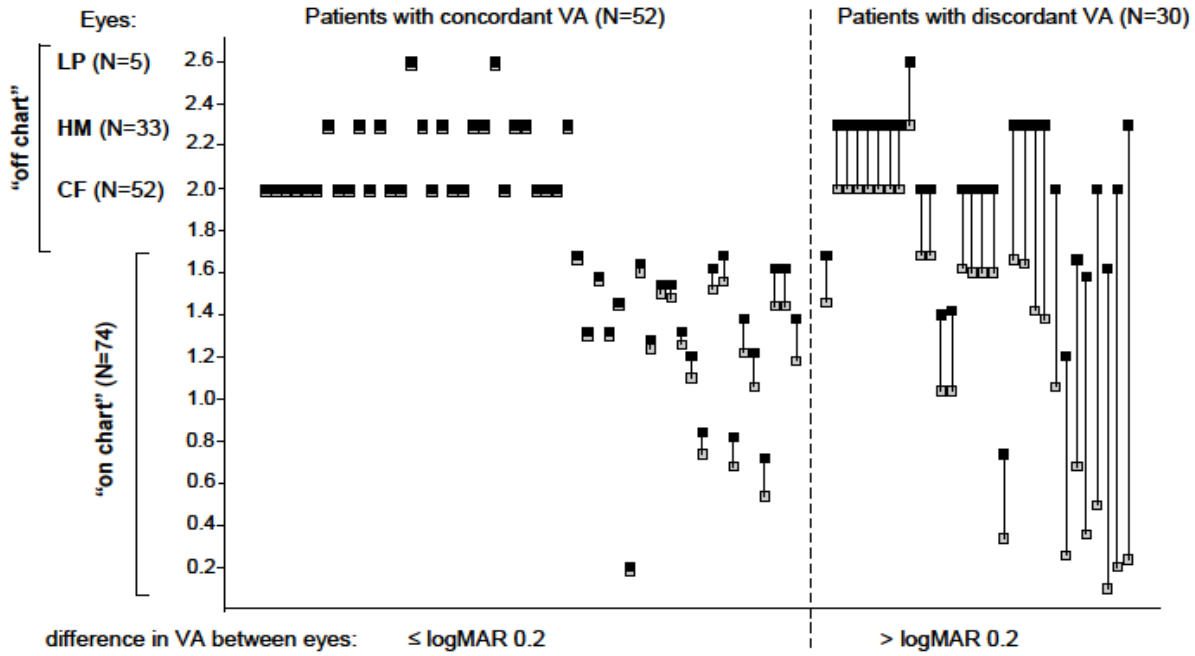
The post hoc analysis conducted in patients with a severely affected vision function ("off-chart patients") suggests a potential benefit of idebenone in this sub-population. Several limitations preclude from achieving valid conclusions (non-predefined nature of the analysis, small number of patients, numeric assignment to a categorical scale). This effect on severely affected patients seems not to be consistent with previous results in patients with initial, less severe stages of the disease given the mechanism of action invoked for idebenone as a protective agent against the nerve damage. This lack of consistency in the benefit obtained in general population makes difficult to identify the true target population that could benefit from this treatment.

No statistically significant difference has been found in QoL, CGI and self-reported energy level using VAS. This suggests that the effect does not appear to be translated into a general perception of benefit of patients.

- **Post-hoc analyses for patients with discordant VA**

The original objective of this study was to determine whether idebenone could mitigate visual loss in the initially least affected eye, however no patients were recruited with the originally defined inclusion criteria. When the inclusion/exclusion criteria were relaxed to include subjects with an onset of LHON within the last 5 years, 30 subjects (36.6% of the ITT population) with one less affected eye, i.e. in an earlier stage of the disease, were recruited (20 on idebenone and 10 on placebo). These patients were defined as having an asymmetrical visual deficit of a > 0.2 logMAR (> 10 letters) difference in VA between the best and the worse eye, i.e. a "discordant VA". Subjects with a bilateral, symmetrical loss of VA had a "concordant VA" and were likely in a more chronic phase of the disease. The definition of discordant VA is acknowledged since the clinically relevant difference in VA between eyes indicates that one of the eyes is clearly less affected and that patients not yet reached the chronic phase of the disease. (see figure 4)

Figure 4. Visual Acuity at Baseline (ITT population)



Source: Listing 14.2-1.1
Both eyes are shown for each patient, connected by a solid line (grey squares: eye with better VA; black squares: eye with worse VA).
VA = Visual acuity; LP: Light perception; HM: Hand motion; CF: Counting fingers

A marked worsening in best VA between Baseline and Week 24 for patients receiving placebo was observed while patients on idebenone maintained stable or improved with an estimated mean difference between treatment groups was equivalent to 21 letters (p=0.003) favouring idebenone. The difference between groups was driven mainly by the worsening in the placebo group (see table 11.).

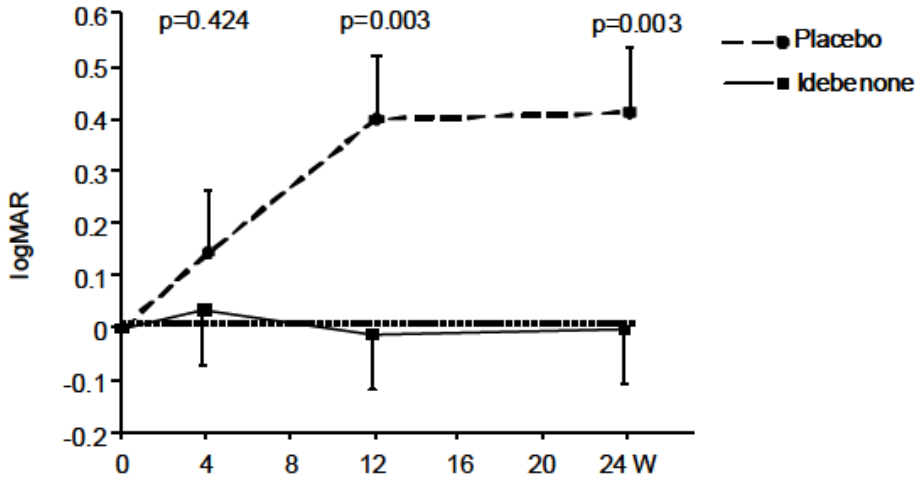
Table 11. Main Secondary Endpoint: Best VA (Subgroup of Patients with Discordant VA)

Change Baseline to	Estimated Change[1] (95% CI) [estimated change in letters]		Estimated Difference[1] ± SEM (95% CI) [difference in letters]	p-value
	Idebenone	Placebo	Idebenone vs. Placebo	
N	20	10		
Week 4	0.032 (-0.174, 0.238) [-1 letter]	0.141 (-0.099, 0.382) [-7 letters]	-0.109 ± 0.135 (-0.381, 0.162) [5 letters]	0.423
Week 12	-0.014 (-0.222, 0.195) [+0 letters]	0.366 (0.131, 0.601) [-18 letters]	-0.380 ± 0.133 (-0.648, -0.112) [19 letters]	0.006
Week 24	-0.011 (-0.218, 0.196) [+0 letters]	0.410 (0.165, 0.654) [-20 letters]	-0.421 ± 0.135 (-0.692, -0.150) [21 letters]	0.003
[2]Week 4-24	0.002 (-0.190, 0.195) [-0 letters]	0.306 (0.096, 0.515) [-15 letters]	-0.303 ± 0.110 (-0.531, -0.076) [15 letters]	0.011

Similar results were observed for patients with mutations G11778A and G3460A where a difference equivalent to 22 letters was observed (p=0.003).

In the change in VA in the eye with the best VA at Baseline patients on idebenone remained stable during the 24-week study while patients on placebo deteriorated in VA (-20 letters; p=0.003). Again, similar results were found when patients with mutations G11778A and G3460A were analysed (mean treatment difference equivalent to 22 letters; p=0.003) (see figure 5).

Figure 5. Change overtime in Best VA (Subgroup of Patients with Discordant VA)



In all analyses the difference in effect between treatment arms was mainly at the expense of the deterioration of VA in the placebo arm.

Ancillary analyses

The applicant has performed additional sub-group analyses on RHODOS data in the attempt to identify the LHON sub-population that would mostly benefit from idebenone treatment and demonstrate the reliability of the results in the as such identified LHON sub-population.

- **Sub-group analyses supporting the idebenone's effect in "Patients with Leber's Hereditary Optic Neuropathy (LHON) due to G11778A or G3460A mitochondrial DNA mutations presenting for treatment within one year of onset of symptoms"**

A sub-group of patients with mutations G11778A or G3460A was identified by the applicant representing a population "at risk" of disease progression or those who may be able to recover visual acuity if treated early. ("Patients with Leber's Hereditary Optic Neuropathy (LHON) due to G11778A or

G3460A mitochondrial DNA mutations presenting for treatment within one year of onset of symptoms").

This proposal is based on the results from 24 patients (11 with discordant VA and 13 with concordant VA). An additional patient with concordant VA was considered as outlier and excluded from the analysis. The Applicant identified patient 23 (mutation G 11778A), a patient that spontaneously gained VA before start of study. Although the chance of visual recovery for this mutation is described to be the lowest in comparison with the other two common mutations, it has been reported to occur. Since the patient regained full vision with an improvement starting before screening and randomisation, it seems highly likely that this subject recovered spontaneously. Exclusion of this outlier is based on medical grounds as, in contrast to the other subjects in the study, patient 23 gained full recovery of visual acuity, a recovery that started before treatment was initiated.

Table 12. The influence of patient 23 on the primary and main secondary end-points in RHODOS

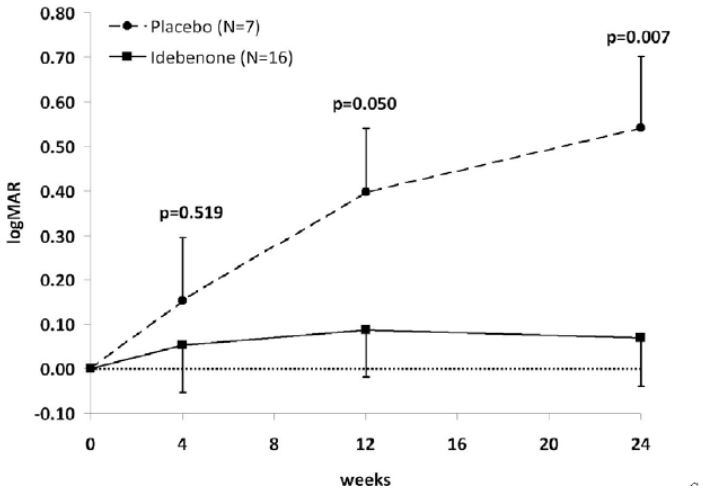
Estimated difference from Baseline to Week 24 (MMRM)		Patients		Best Recovery			Best Acuity		
		N	Ide/Pla	logMAR	letters	p-value	logMAR	letters	p-value
p-value <= 0.10	ITT	82	53 / 29	-0.064	3	0.291	-0.120	6	0.078
p-value <= 0.05	ITT; excl. P23	81	53 / 28	-0.100	5	0.086	-0.160	8	0.015
	Subgroup with G11778A or G3460A	65	42 / 23	-0.092	4	0.187	-0.169	8	0.037
	Subgroup with G11778A or G3460A; excl. P23	64	42 / 22	-0.144	7	0.031	-0.224	11	0.004
	Subgroup with G11778A or G3460A; Onset < 1 y	24	16 / 8	-0.079	3	0.540	-0.282	14	0.138
	Subgroup with G11778A or G3460A; Onset < 1 y; excl. P23	23	16 / 7	-0.212	10	0.063	-0.474	23	0.007

From the above table it can be seen that Patient 23 has had a very profound confounding influence on the outcome both for the primary and main secondary endpoints (Estimated difference from Baseline to Week 24 for Best Recovery: ITT: p=0.291; ITT excl. P23: p=0.086 and Best Acuity: ITT: p=0.078; ITT excl. P23 p=0.015). With the exclusion of Patient 23 from the analysis for the pre-specified population of patients with LHON due to either the G11778A or G3460A mtDNA mutations, the difference in outcome at Week 24 between idebenone and placebo-treated patients becomes significant for both the primary Best Recovery (p=0.031) and main secondary Best Visual Acuity (p=0.004) endpoints.

Similarly, the outcome for the proposed Target Population (Patients with Leber's Hereditary Optic Neuropathy (LHON) due to G11778A or G3460A mitochondrial DNA mutations presenting for treatment within one year of onset of symptoms) also becomes highly significant for the Best VA endpoint (p=0.007) with the treatment effect increasing from 14 to 23 letters, which are clinically meaningful treatment effect sizes.

Depending on the assigned treatment (placebo or idebenone) a different evolution along the course of the study was observed. Whereas patients on idebenone followed a visual acuity "stabilisation pattern" mean visual acuity was progressively impaired in patients receiving placebo (see figure 6 below).

Figure 6. Change over time in Best VA in patients with either G11778A or G3460A mutation and onset of symptoms under 1 year



- **Sub-group analyses supporting the idebenone's effect in "Patients with Leber's Hereditary Optic Neuropathy (LHON) presenting for treatment within one year of onset of symptoms"**

In order to address the CHMP concerns related to the post-hoc nature of the proposed target population a new target population has been defined by the Applicant, corresponding to patients presenting for treatment within one year of treatment regardless of the mutation type. The revised Target Population (referred from now on as "target population") , including all patients irrespective of mutation, would be identical to the sub-group of patients with disease history of less than 1 year, which was an analysis sub-group pre-specified in both the RHODOS protocol and SAP. This should therefore eliminate the concern that the Target Population was derived from post-hoc analysis.
It should be noted that patient 23 was excluded from this population based on the considerations given above (outlier based on medical grounds)

The outcome for this Target Population (Onset ⩽ 1 y; ITT*) is shown in table 13. The outcome for Best VA for the ITT* population and the population with Onset ⩽ 1 y; G11778A or G3460A* (Target Population against which the major objection was raised) are shown for comparison.

Table 13. Analyses of change from baseline to week 24 for best VA and for individual eyes

	Patients	Best VA, BL to Week 24			Eyes	Individual Eyes, BL to Week 24		
	N#	logMAR	letters	p-value	N#	logMAR	letters	p-value
ITT*	81 (53/28)	-0.160	8	0.015	162 (106/56)	-0.138	6	0.001
Onset ≤ 1 y; G11778A or G3460A*	23 (16/7)	-0.474	23	0.007	46 (32/14)	-0.371	18	<0.001
Revised Target Population: Onset ≤ 1 y; ITT*	28 (19/9)	-0.342	17	0.016	56 (38/18)	-0.268	13	0.002

Total (SAN Idebenone/Placebo)

* Data shown excluding patient 23

Data show the treatment difference between SAN Idebenone and placebo from Baseline to Week 24, estimated using a mixed model of repeated measures

Whilst patients carrying the T14484C mutation were previously excluded to eliminate the potentially confounding effect of the high rate of spontaneous VA recovery reported in these patients (Yu-Wai-Man et al., 2009; Fraser et al., 2010), it can be seen that the re-inclusion of these patients reduces treatment effect size from 23 letter (for Onset ⩽ 1 y; G11778A or G3460A*) to 17 letters for the Best VA endpoint in the Target Population (Onset ⩽ 1 y; ITT*). These results also show consistency with other related outcomes (such as the response by individual eyes count) and, in general, with respect to the previously submitted results.

The Applicant has provided a comparison between the RHODOS ITT population and the revised target population (LHON patients presenting within 1 year of onset of symptoms) in terms of demographic characteristics in order to show that the two populations are comparable. (see table 14 below)

Table 14 Baseline demographics for the target population and RHODOS ITT population

		Revised Target Population (Onset ≤ 1 y; ITT*)			ITT*		
		SAN Idebenone	Placebo	Total	SAN Idebenone	Placebo	Total
Patients	N	19	9	28	53	28	81
Age at BL [years]	Mean	34.9	26.2	32.1	33.7	33.0	33.5
	SD	16.7	12.6	15.8	14.5	14.6	14.4
	Median	32.0	21.0	26.0	30.0	27.0	29.0
	Min	14.0	14.0	14.0	14.0	14.0	14.0
	Max	63.0	47.0	63.0	63.0	66.0	66.0
Age at onset [years]	Mean	34.2	25.6	31.5	31.8	31.0	31.5
	SD	16.6	12.4	15.7	14.8	14.4	14.6
	Median	31.1	20.0	25.5	26.4	25.7	26.2
	Min	13.4	13.4	13.4	13.5	12.8	12.8
	Max	62.3	46.1	62.3	62.3	64.6	64.6
Time since onset at BL [years]	Mean	0.68	0.59	0.65	1.9	2.0	1.9
	SD	0.24	0.29	0.26	1.4	1.4	1.4
	Median	0.71	0.56	0.67	1.5	1.7	1.6
	Min	0.22	0.16	0.16	0.2	0.2	0.2
	Max	1.00	1.00	1.00	5.1	4.7	5.1
% Patients with Mutation	G1177A	74%	67%	71%	66%	64%	65%
	G3460A	11%	11%	11%	13%	14%	14%
	T14484C	16%	22%	18%	21%	21%	21%
Best VA at BL [logMAR]	Mean	1.60	1.38	1.53	1.61	1.60	1.60
	SD	0.61	0.72	0.64	0.64	0.59	0.62
	Median	1.60	1.56	1.60	1.64	1.68	1.68
	Min	0.24	0.10	0.10	0.18	0.10	0.10
	Max	2.60	2.30	2.60	2.60	2.30	2.60
VA at BL (all eyes) [logMAR]	Mean	1.76	1.60	1.71	1.75	1.71	1.74
	SD	0.55	0.59	0.56	0.58	0.52	0.56
	Median	2.00	1.64	1.68	2.00	2.00	2.00
	Min	0.24	0.10	0.10	0.18	0.10	0.10
	Max	2.60	2.30	2.60	2.60	2.30	2.60

Revised Target Population: Patients presenting within 1 year of onset of symptoms

ITT*: RHODOS ITT excluding patient 23

- **Analyses carried out in order to rule out "spontaneous stabilisation" as a confounder of the effect**

Three patients within the Target Population presented at Baseline with residual VA in one eye. Whilst in these patients the loss of VA in the first affected eye appears consistent with the natural history of the disease, the loss of VA in their second eyes appears to be delayed beyond what might otherwise have been expected. The demographics of these patients are similar with respect to those characteristics known or suspected to affect the natural history of LHON (time since onset at Baseline, LHON mutation type, age at presentation, smoking status).

None of them carries the LHON mutation associated with a more benign prognosis (T14484C).

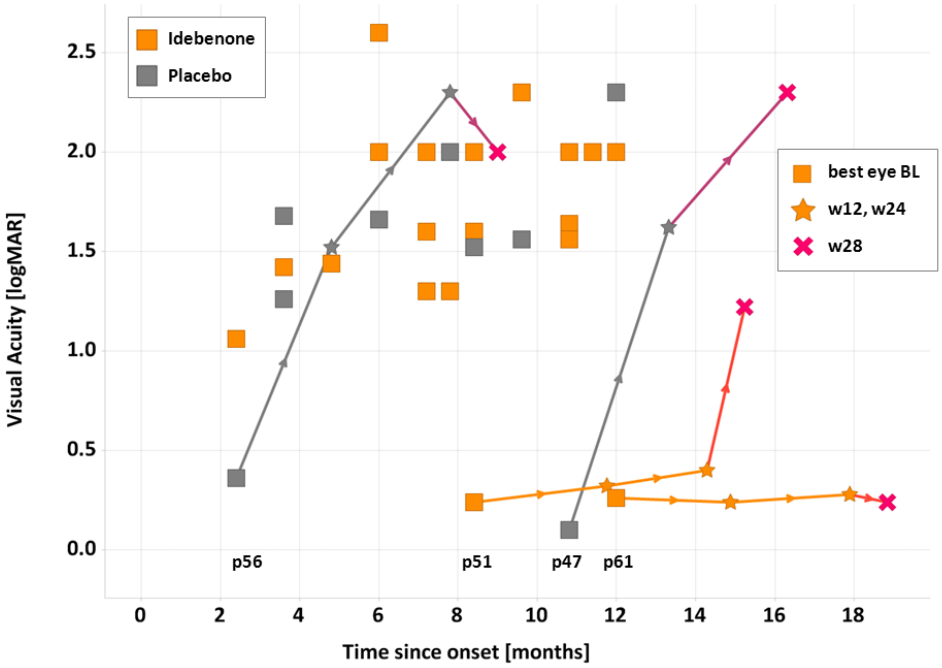
The VA outcomes for these patients are shown in figure 6. The VA of placebo-randomised patient 47 deteriorated after Baseline and at follow-up presented with further deterioration. Idebenone-randomised patients 51 and 61 remained stable however up to Week 24. Since at Baseline idebenone-

randomised patients 51 and 61 were separated with respect to time since disease onset by placebo-randomised patient 47, time since onset of symptoms at Baseline does not appear to have influenced the outcome for these patients. The difference in outcome for these patients can be attributed to the effect of treatment with idebenone.

The rapid deterioration in the VA of patient 51 after discontinuation of idebenone therapy, also does not support the suggestion that the VA of this patient may have "spontaneously stabilised", and followed a more benign disease course than might otherwise have been expected.

Patients 47, 51 and 61 were characterised by good residual VA at Baseline. Placebo-randomised patient 56 also presented with good VA at Baseline but disease in this patient progressed as expected from the natural history of LHON.

Figure 6. VA outcomes for Target Population patients 56, 51, 47 and 61



Despite the fact that there was no identifiable Baseline characteristic that might have been expected to result in milder disease progression or improved outcome for idebenone-randomised patients 51 and 61, as suggested, the Applicant has assessed the contribution of these patients to the overall outcome in the proposed Target Population. The estimated treatment effect size and p-value are slightly affected when excluding these patients, but a clinically relevant treatment effect remains (Table 15).

Table 15. Treatment effect size in the proposed Target Population excluding idebenone-randomised patients 51 and 61

	Change in best VA from BL to W24 (MMRM)				
	Patients	Ide/Pla	best VA	letters	p-value
Target Population	28	19/9	-0.342	17	0.016
Target Population excl. p51, p61	26	17/9	-0.241	12	0.069

- **Analyses carried out in order torule out spontaneous recovery as a confounder of the effect**

Responder analyses on ITT and target populations

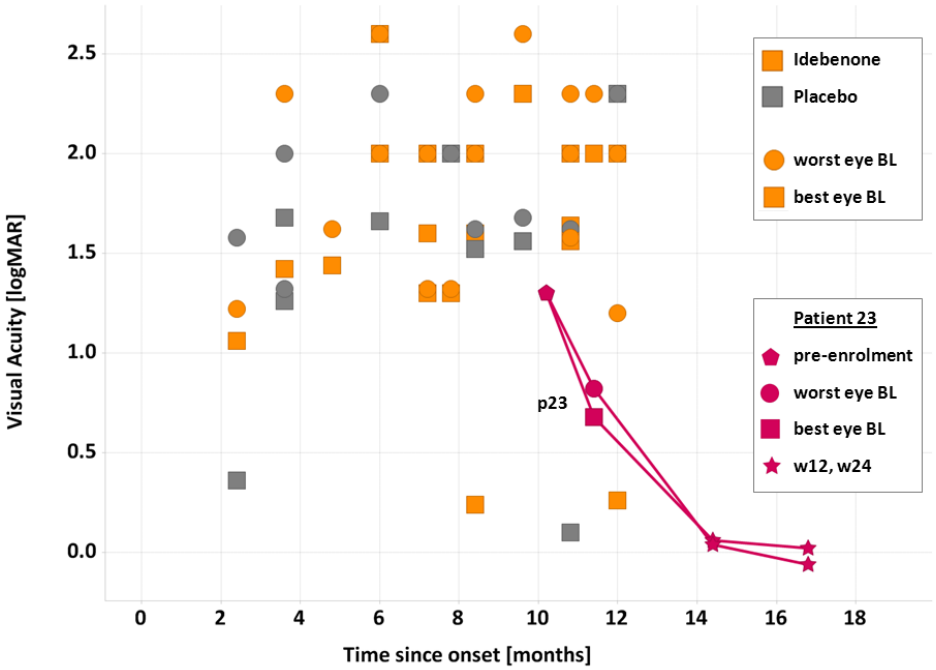
A responder analysis has been conducted in order to investigate the incidence of any improvement in VA prior to treatment for both the idebenone and placebo treated patients within the ITT and Target Populations and has analyzed the influence of this on subsequent VA outcomes. In order to ensure that the contribution of any improvement in any eye is taken into consideration (rather than including only the Best eye at Baseline (BL) or only the eye with the Best Recovery), the Applicant calculated the number of eyes for which the VA shows any improvement at various time-points subsequent to the Screening (SC) visit in RHODOS including SC→BL, BL→W24 (Week 24) and BL→OFU. The change in VA and the count of eyes for which VA improves between BL and W24 were pre-specified secondary analyses in RHODOS

The results suggest that the proportion of eyes improving and the magnitude of the improvement BL→W24 and BL→OFU was higher in those randomized to idebenone compared to those randomized to placebo.

Potential effect of "spontaneous improvement" on the outcome in the proposed Target Population

Spontaneous improvement presents as a rapid and extensive recovery of vision (Stone et al., 1992). Such recovery of VA was observed in RHODOS in placebo-randomised patient 23. As can be seen in Figure 7, the VA of patient 23 recovered dramatically prior to Baseline in RHODOS and continued to improve until normal VA was recovered at Week 12 and maintained thereafter (patient 23 was identified as a natural history confounder and excluded from the ITT and Target Population).

Figure 7. Baseline VA of patients in the Target Population overlaid with an example of spontaneous recovery (patient 23)



No recoveries as extensive and as rapid as those reported to occur spontaneously (as evidenced by patient 23 in RHODOS) were observed in the idebenone-treated patients within the Target Population.

The Applicant has assessed all clinically relevant improvements (equivalent to 10 letters or more) in VA which occurred between Baseline and Week 24 in the Target Population. These are presented in Figure 8. Such improvements in VA were only observed in the idebenone-treated group (6 of 19 patients) and in none of the 9 patients in the placebo group within the Target Population. This suggests that such recoveries in VA are associated with idebenone treatment, rather than with "spontaneous recovery". Remarkably, only 1 of the 6 patients with clinically relevant improvement in VA carried the T14484C mutation; all others had the G11778A or G3460A mutations, not typically associated with spontaneous recovery.

Figure 8. Patients in the Target Population with clinically relevant improvement in VA between Baseline and Week 24

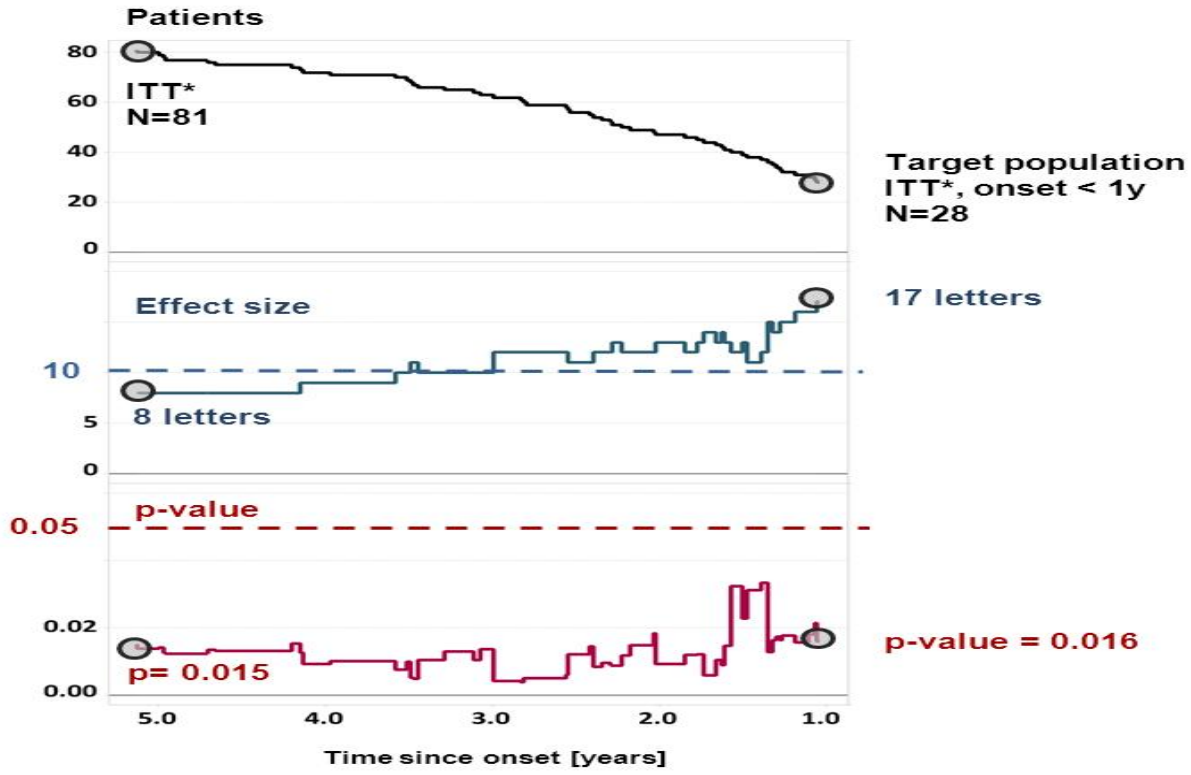
p39	p40	p45	p61	p72	p81
G11778A	G11778A	G3460A	G11778A	G3460A	T14484C
age 19	age 62	age 23	age 63	age 16	age 63
smoker	smoker	smoker	smoker	smoker	non-smoker

In addition to the improvement observed in idebenone-treated patients between Baseline and Week 24, the proportion of patients and eyes worsening was reduced in idebenone-treated patients.

- **Comparison of the treatment effect size and associated p-value for populations of patients in RHODOS based on time since onset of symptoms at Baseline**

This significant p-value suggests that the outcome for the proposed Target Population was not a chance finding. In order to provide evidence that the outcome in the Target Population was associated with a general treatment effect in idebenone-treated patients, this outcome was analysed using a procedure which allows the treatment effect size and p-value to be measured throughout the ITT* population (Figure 9).

Figure 9. Comparison of the treatment effect size and associated p-value for populations of patients in RHODOS based on time since onset of symptoms at Baseline



ITT population (ITT excluding natural history confounder patient 23*)

This analysis shows that in the ITT* population (n=81), the treatment effect size was 8 letters and the p-value 0.015. Moving from left to right across all 3 graphics, sequentially removing those patients with the longest time since onset of symptoms at Baseline, shows that the clinically relevant treatment effect size of 10 letters is exceeded after excluding the approximately 20 patients with time since onset of symptoms at Baseline of more than 3 years.

In all populations to the right of this point (i.e. those with shorter time between symptom onset and Baseline), the treatment effect size increases steadily whilst the p-value remains stable and significant until the Target Population (pre-specified subgroup of RHODOS patients treated within 1 year of onset of symptoms) is reached on the far right hand side of the graphic (treatment effect size 17 letters, p=0.016).

The increasing effect size observed moving from left to right also serves to illustrate the published observation (Carelli et al., 2011), that patients with shorter time since onset of symptoms are more likely to benefit from treatment with idebenone. Importantly, the constant nature of the p-value and the increase in treatment effect size show that the treatment effect was not due to the contribution of individual patients but is a general treatment effect.

Summary of main study

The following table summarise the efficacy results from the main study supporting the present application. These summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 16. Summary of Efficacy for RHODOS trial

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 (RHODOS)			
Study identifier	SNT-II-003		
Design	Double-blind, randomized, placebo-controlled, parallel group study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	3 years (07 April 2007 (first subject screened) to 19 February 2010 (last subject completed)) not applicable not applicable	
Hypothesis	To determine whether administration of idebenone can improve visual function in Leber's Hereditary Optic Neuropathy (LHON) patients		
Treatments groups	Idebenone		Idebenone 900 mg/day, 53 patients with valid VA data, 24 weeks of treatment
	Placebo		Placebo, 29 patients with valid VA data, 24 weeks of treatment
Endpoints and definitions	Primary endpoint	Best Recovery in VA	Best recovery of logMAR VA between baseline and week 24 in either right or left eye
	Main Secondary endpoint	Change in Best VA	Best visual acuity at Week 24 (best eye at Week 24) compared to best visual acuity at Baseline (best eye at Baseline)
	Other Secondary endpoint	Change in VA in all eyes	Change in VA between BL and Week 24 for all eyes (treated as independent)
	Responder analysis (A): for patients entering the trial with an eye still less affected than 0.5 logMAR: Count of patients in which the visual acuity in the initially least affected eye does not deteriorate to 1.0 logMAR or more		
	Responder Analysis (B): for patients with "off-chart" VA with both eyes at Baseline: Count of eyes/patients for which the VA improves to reading at least 5 letters "on-chart" (i.e. ≤logMAR 1.60) at Week 24		
Database lock	28 May 2010		

<u>Results and Analysis</u>

Analysis description	**Primary Analysis**		
	ITT* population: excludes one patient identified as natural history confounder (N=53 for idebenone group; N=28 for placebo group). Analysis using MMRM model.		
Descriptive statistics and estimate variability	Treatment group	Idebenone 900 mg/day	Placebo
	Best recovery in VA (mean ± se)	logMAR -0.136 ± 0.039	logMAR -0.036 ± 0.051
	Change in Best VA (mean ± se)	logMAR -0.037 ± 0.043	logMAR 0.123 ± 0.057
	Change in VA of all eyes (mean ± se)	logMAR -0.056 ± 0.028	logMAR 0.082 ± 0.038
	Responder analysis (A)	0 of 6	2 of 2

	Responder Analysis (B)	7 of 25 patients 12 of 61 eyes	0 of 13 patients 0 of 29 eyes
Effect estimate per comparison Idebenone group vs. Placebo group	Primary endpoint: Best recovery in VA	estimated means (95% CI)	logMAR -0.100 (-0.214; 0.014)
		P-value	0.086
	Main secondary endpoint: Change in Best VA	estimated means (95% CI)	logMAR -0.160 (-0.289; -0.031)
		P-value	0.015
	Secondary endpoint: Change in VA of all eyes	estimated means (95% CI)	logMAR -0.138 (-0.222; -0.054)
		P-value	0.001
	Responder analysis (A)	p-value using Fisher's exact test	0.036
	Responder Analysis (B)	p-value using Fisher's exact test: for patients for eyes	 0.072 0.008
Notes	Responder Analysis (B) was a post-hoc analysis		
Analysis description	**Secondary Analysis**		
	Subgroup of ITT* population (excluding one patient identified as natural history confounder): patients with time since onset of symptoms ≤ 1 year (N=19 for idebenone group; N=9 for placebo group.) Analysis using MMRM model.		
Descriptive statistics and estimate variability	Treatment group	Idebenone 900 mg/day	Placebo
	Best recovery in VA (mean ± se)	logMAR -0.093 ± 0.060	logMAR 0.060 ± 0.087
	Change in Best VA (mean ± se)	logMAR 0.051 ± 0.087	logMAR 0.394 ± 0.124
	Change in VA of all eyes (mean ± se)	logMAR 0.003 ± 0.053	logMAR 0.271 ± 0.076
Effect estimate per comparison Idebenone group vs. Placebo group	Primary endpoint: Best recovery in VA	estimated means (95% CI)	logMAR -0.154 (-0.346; 0.039)
		P-value	0.116
	Main secondary endpoint: Change in Best VA	estimated means (95% CI)	logMAR -0.342 (-0.618; -0.067)
		P-value	0.016
	Secondary endpoint: Change in VA of all eyes	estimated means (95% CI)	logMAR -0.268 (-0.435; -0.102)
		P-value	0.002
Notes	The subgroup of patients with time since onset of symptoms ≤ 1 year was pre-specified in the study protocol and statistical analysis plan.		

Analysis performed across trials (pooled analyses and meta-analysis)

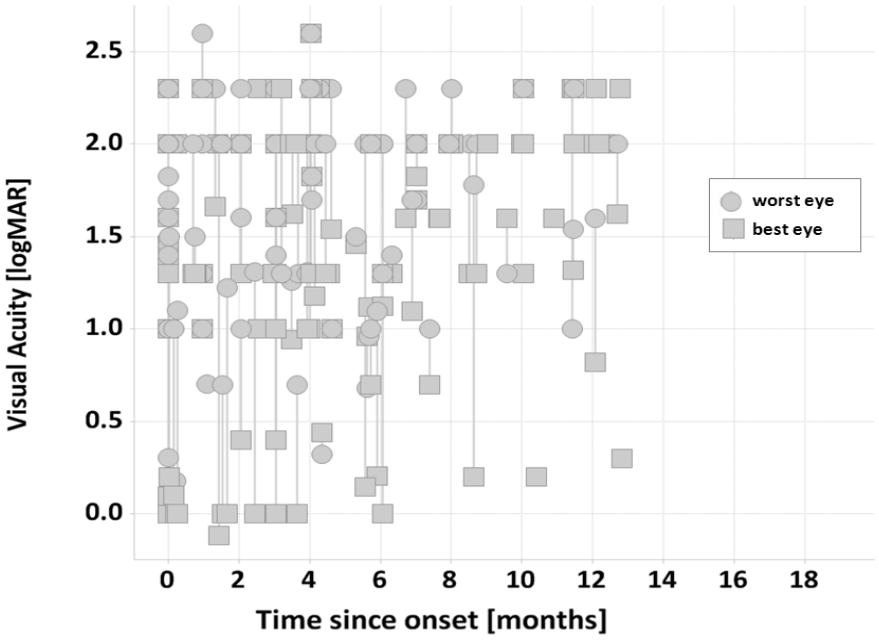
At the CHMP request the applicant has performed various meta-analyses across available literature data in LHON patients. The aim of the analyses was to provide additional scientific evidence that would support the efficacy findings reported in RHODOS study.

- **Natural History of LHON – Rapid progression to bi-lateral vision loss**

The usual presentation of LHON is an otherwise unexplained colour desaturation and rapid loss of central vision in one eye, followed by similar loss of vision in the fellow eye within days or months of the first onset of symptoms (Carelli et al., 2004; Newman, 2005; Yu-Wai-Man et al., 2009). More than 97% of patients develop second eye involvement within one year (Newman, 1991; Riordan-Eva et al., 1995; Fraser et al., 2010).

Natural history data from 95 LHON patients available from cohort studies, case reports and from natural history data collected from RHODOS patients not included in the Target Population was analysed. These data are presented in Figure 10. In agreement with the published literature, it can be seen that LHON patients experience rapid vision loss in both eyes. The vast majority of patients have progressed to logMAR ≥ 1.0, a commonly accepted threshold for legal blindness, in both eyes within six months of initial onset of symptoms.

Figure 10. Natural history of LHON: Change in VA with time since onset of symptoms



Available literature data on spontaneous recovery of VA

Generally, recovery in VA of LHON patients over time is rare, but depending on the disease-causing mtDNA mutation, differences have been described. Patients with the G11778A mutation clearly have the worst prognosis with an expected spontaneous recovery rate of 4 23% (Table 17), followed by patients with the G3460A mutation and patients with the T14484C mutation having the highest probability of spontaneous improvement in VA.

Table 17. Differential rates of spontaneous VA recovery reported for carriers of the primary mtDNA mutations in LHON

LHON Mutation	Reported spontaneous recovery rate	Reference (primary sources only)
G11778A	4%[1] 4%[2] 4%[3] 22%[1] (9%<1y; 5%1-4y; 9%>4y) 23%[6]	Newman et al. (1991). Am. J. Ophthalmol. 111:750 Riordan-Eva et al. (1995). Brain 118:319 Stone et al. (1992). J. Clin. Neuroophthalmol. 12:10 Spruijt et al. (2006). Am. J. Ophthalmol. 141: 676 Carelli et al. (2011). Brain 134: e188
G3460A	15%[1] (8%<1y; 8%1-4y) 20%[4] 25%[2]	Spruijt et al. (2006). Am. J. Ophthalmol. 141; 676 Johns et al. (1992). Arch. Ophthalmol. 110:1577

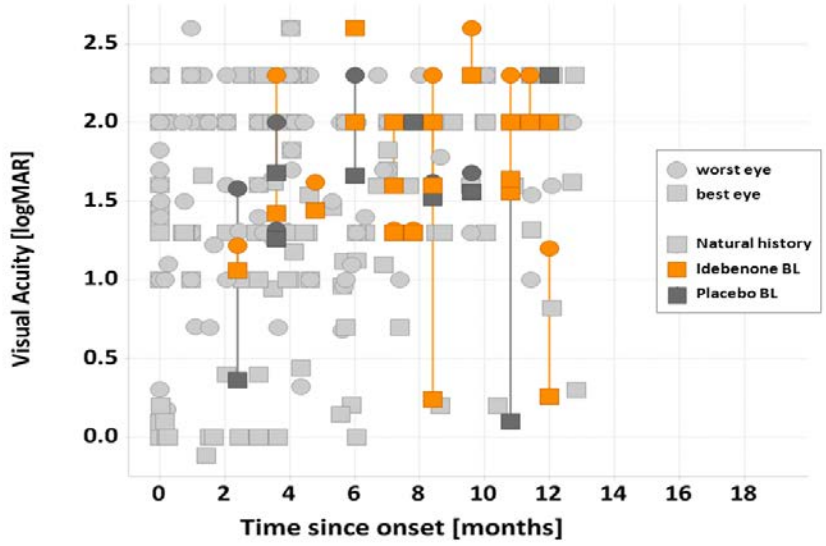
		Riordan-Eva et al. (1995). Brain 118:319
T14484C	37%[5]	Johns et al. (1993). Arch. Ophthalmol. 111:495
	50%[2]	Riordan-Eva et al. (1995). Brain 118:319
	58%[1]	Macmillan et al (1998). Neurology 50:417
	64%[1] (16% <1y; 30%1-4y; 19%>4y)	Spruijt et al. (2006). Am. J. Ophthalmol. 141; 676
	71%[1]	Harding et al. (1995). Muscle & Nerve 3; S82

As usually understood, spontaneous recovery of vision in LHON is the rapid and dramatic improvement in VA (occurring within days to few weeks) which can result in complete VA recovery, essentially representing a reversal of the rapid VA loss which initially occurred (Stone et al., 1992).

The VA of patients within the Target Population compared with the VAs expected from the natural history of LHON

The Baseline VA for all eyes of patients within the Target Population are shown overlaid on the data presented for the natural history of VA in LHON gathered from other sources (Figure 11). In patients within the Target Population, differences in the VA at Baseline of any patient's individual eyes are shown by circles (worst eye) and squares (best eye) linked by a line. As can be seen, at Baseline, the majority of patients within the Target Population showed the expected pattern of rapid bi-lateral vision loss, consistent with the natural history for LHON as reported above and previously in the literature (Newman, 1991; Riordan-Eva et al., 1995; Carelli et al., 2004; Newman, 2005; Yu-Wai-Man et al., 2009). It would therefore be expected that the post-Baseline natural history of patients within the Target Population should follow a path to permanent vision loss, with spontaneous recovery occurring only rarely.

Figure 11. Baseline VA of patients within the proposed Target Population compared to the observed VA by time since onset of symptoms according to the natural history of LHON



Data from the previous Figure 10 (line connecting eyes removed for clarity) are shown overlaid with data from the Target Population (with connecting lines).

- **Efficacy analyses of idebenone in LHON in the published data**

Overview of available retrospective cohort studies and case reports from the literature

Three retrospective open-label cohort studies and 7 case reports are currently available in the published literature (Appendix 1: Tabulated summaries, Appendix 2: Abbreviated narratives), collectively reporting on the VA outcome of 143 LHON patients treated with idebenone (Table 18). The majority (89.5%) of patients described in these studies were from Europe (Italy, France, Spain, Serbia).

In combination with the 53 idebenone-treated patients from RHODOS, which is the only placebo-controlled study conducted so far, efficacy data are available from 196 LHON patients under idebenone treatment.

Seven of the 10 studies/case reports available in the literature enrolled 67 patients with onset of symptoms ≤ 1 year prior to idebenone treatment and carrying any of the three primary LHON mtDNA mutations (G11778A, G3460A or T14484C), thereby corresponding to the proposed Target Population. Together with the 19 idebenone-treated patients reported for RHODOS, efficacy data are available from 86 patients corresponding to the proposed Target Population.

Table 18. Available literature reports with idebenone in LHON

Author/Study	Treated patients	Time from symptom onset at start of therapy	Study type	Treatment duration	Idebenone dose (mg/day)	Control group (untreated)
Mashima 1992	1	n.a	CR	1 yr	90	--
Carelli 1998a	6	3 pts ≥ 5yrs 3 pts ≤ 1yr	CR*	1 yr	135-360	--
Carelli 1998b	1	≤ 1yr	CR*	6 mo	270	--
Mashima 2000	14	≤ 1yr	RS*	≥ 1 yr	180	14
Carelli 2001	2	≤ 1yr	CS*	7-11 mo	270-675	--
Barnils 2007	2	≤ 1yr	CS*	1 yr	270	--
Jancic 2011	9	n.a.	CS	≤ 1 yr	135	--
Carelli 2011	44	≤ 1yr	RS*	~ 5 yrs	270-675	59
S.Peyman 2012	1	≤ 1yr	CS*	9 mo	900	--
Orssaud 2012	63	n.a.	RS	2 yrs	270	--
Total	***143***					

CS: case report; RS: retrospective cohort studies; RS*/CS*: studies in patients with symptom onset ≤ 1 year prior to idebenone treatment and any of the three LHON mtDNA mutations G11778A, G3460A or T14484C, i.e. representative of the proposed Target Population. n.a.: not available. y: year(s). mo: months. pts: patients.

Across all 10 available reports, the duration of treatment ranged from 6 months up to 5 years, with 131 patients (91%) treated for at least 12 months.

The idebenone doses used in these 10 reports ranged from 90 mg/day to 900 mg/day with a majority of patients receiving 270-675 mg/day. Three of the 10 reports state that patients received vitamin C and vitamin B2 or B12 in addition to idebenone, in one case study the concomitant use of CoQ10 is reported (Appendix 1).

The retrospective studies conducted in Italy (Carelli et al., 2011) and Japan (Mashima et al., 2000) compared VA outcomes from a total of 58 idebenone-treated LHON patients enrolled within 1 year from symptom onset with 73 untreated patients of similar profile. All other publications described the development of VA and other ophthalmologic assessments from a total of 85 idebenone-treated patients without in-study comparators.

Although all three retrospective cohort studies were comparable with respect to patient demographics (Table 19), the retrospective study by Carelli (2011) is the most informative open-label study

published to date, based on the number of patients included, the comparison to an untreated in-study control group and the level of analyses undertaken.

Table 19. Patient demographics across retrospective cohort studies

	Mashima 2000	Carelli 2011	Orssaud 2012
Patients treated with idebenone	14	44	63
Average age at onset of symptoms	23 years	26 years	28 years
% male	86%	84%	89%
% patients with G11778A mutation	79%	68%	78%

For patients in the Orssaud (2012) study the time since symptom onset prior to idebenone treatment was not specified and therefore it is not known whether patients from this study are comparable with those in the proposed Target Population. Consequently, this study has not been considered further for this summary, even though the study outcome is supportive of an idebenone treatment effect.
The authors report that 30.15% (19 of 63) of patients treated with idebenone for 24 months showed recovery in VA from mean logMAR 1.461 for both eyes at start of treatment to logMAR 0.673 at the end of the treatment. Importantly, 68% of patients with improved vision carried the G11778A mutation (see Appendix 2 for details).

Comparative efficacy analyses of literature case reports and retrospective cohort studies for patients treated ≤ 1 year after onset of symptoms and carrying any of the three primary LHON mtDNA mutations

Data from 143 patients treated with idebenone are reported in the published literature. Of these, 67 patients were treated ≤ 1 year after the onset of symptoms and therefore correspond to the Target Population. Despite differences in treatment duration and idebenone dose, there is a consistent pattern demonstrating that patients with LHON benefit from idebenone treatment. This idebenone-mediated improvement is best seen in responder analyses, where it was shown that a higher proportion of patients treated with idebenone experienced a clinically relevant (i.e. at least 2 lines) improvement in VA when compared to in-study untreated comparator groups. These findings are of particular relevance for patients with the G11778A mutation, who have the worst prognosis but represent the largest subgroup of patients with LHON in Europe (60-70%). In this group of patients the proportion of patients with this mutation and treated ≤ 1 year after onset of symptoms was ≥2-fold higher for the idebenone-treated patients than the responders in the untreated control group and clearly higher than the upper range of spontaneous rates of recovery reported for the natural history.

Clinical studies in special populations

The applicant has not conducted any clinical studies in special populations. This is considered acceptable, given the overall safety profile of idebenone and the rare disease being treated.

Supportive studies

- **RHODOS Observational Follow-up Study (SNT-II-003-OFU)**

RHODOS-OFU was a single-visit, observational follow-up study of patients who participated in RHODOS, designed to provide additional data on disease progression following discontinuation of study treatment, to allow an assessment of the persistence of any benefit in VA obtained from idebenone treatment during RHODOS.

Furthermore, the planned collection of natural history data in the form of Individual Patient Narratives, would allow comparison of the natural history of individual patients with that expected from reports from the literature.

In RHODOS (SNT-II-003), patients with LHON were randomized to receive Idebenone or placebo for 6 months. Since the last patient completed in February 2010, participating patients received their last dose of study medication between one and a half and three and a half years prior to the start of the RHODOS-OFU. The RHODOS-OFU study aimed to evaluate the current visual acuity of RHODOS participants, for comparison to their Baseline and final VA assessments in RHODOS. An attempt was to be made to assess whether any change in visual acuity had occurred since completing RHODOS and if so, the course of any such changes were recorded. In addition, any medical conditions that may have affected the patient's visual acuity other than LHON were recorded.

From the 85 patients previously participating in RHODOS, 60 were enrolled into RHODOS-OFU, of which 58 provided valid VA data.

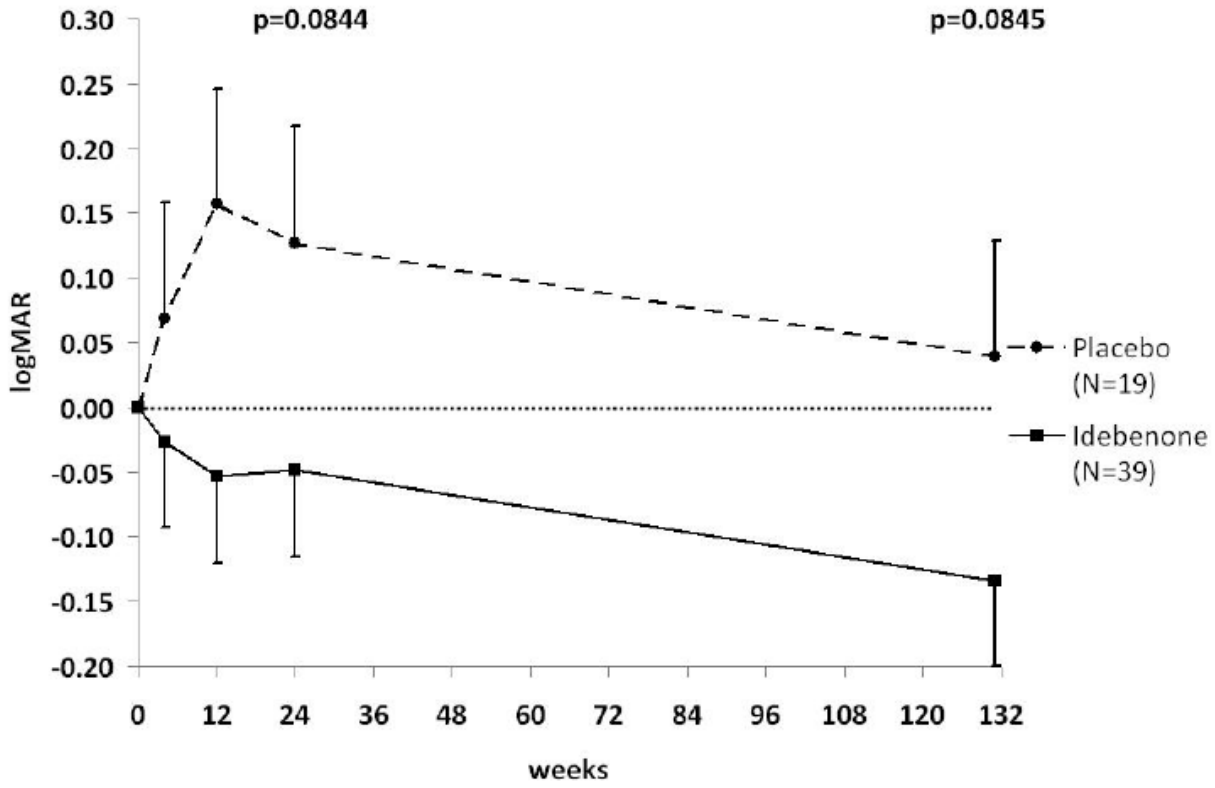
It was understood at the outset that robust analysis of the analysis of VA data may be confounded by the natural history of participating patients and medications taken since leaving RHODOS which may have included idebenone. Therefore, patients were asked to report their medication history since their last RHODOS visit to aid in the interpretation of findings. As the unblinded randomization codes were sent to the Investigators following database lock of RHODOS, the Investigators (and the patients) were unblinded to RHODOS study assignment at the RHODOS-OFU visit.

Results

Primary end-point. Best VA was measured at the RHODOS-OFU visit. For patients in the RHODOS-OFU, the difference between treatment groups at Week 24 in RHODOS was logMAR -0.175, equivalent to 8 letters favouring Idebenone (p=0.0844), compared to logMAR -0.120, equivalent to 6 letters favouring Idebenone (p=0.078) for this endpoint for the ITT population in RHODOS.

Main secondary end-point. Both treatment groups showed almost identical (i.e. parallel) improvements in Best VA between Week 24 of RHODOS and the RHODOS-OFU visit (idebenone: logMAR -0.085, improvement by 4 letters; placebo: logMAR -0.088, improvement by 4 letters). This resulted in a difference between treatment groups at the SNT-II-003-OFU visit of logMAR -0.173, equivalent to 8 letters favouring Idebenone (p=0.0845), which is shown in Figure 12 below.

Figure 12. Change overtime in best VA



For the sub-groups of patients carrying either the G11778A or G3460A mtDNA mutations with onset of disease ≤ 1 year, the difference between treatment groups at the RHODOS-OFU visit were similar to the difference between treatment groups at the end of RHODOS (logMAR -0.203, equivalent to 10 letters favouring Idebenone (p=0.404), versus logMAR -0.282, equivalent to 14 letters favouring Idebenone (p=0.138) for this subgroup from the RHODOS ITT population). As before, both treatment groups showed almost identical improvements in *Best VA* between Week 24 of RHODOS and the RHODOS-OFU visit.

The reasons for the improvement in VA in both treatment groups subsequent to RHODOS have been investigated. This overall improvement appears to be driven by patients who have been more recently diagnosed (i.e. within 1 year prior to enrolment) and it is speculated that as such patients come to terms with their disease, they learn to use their peripheral vision to enable them regain some usable VA ("scanning"). This effect was not seen in patients with established disease (i.e. in patients with disease history more than 1 year prior to enrolment).

A responder analysis was conducted in patients (or eyes) with "off-chart" VA at Baseline of RHODOS. Of the 38 patients with "off-chart" VA at Baseline in RHODOS (25 of whom were randomized to Idebenone, 13 to placebo), 26 were enrolled into RHODOS-OFU (18 and 8 respectively). Of the 7 patients who responded with improvement to "on-chart" VA, data are available on 5, all of whom remained with "on-chart" vision and 4 of whom were still able to read a full line. No patient responded similarly in the placebo group. Of the 18 non-responding patients in RHODOS data was available on 13. Of these, 5 had responded by the RHODOS -OFU visit. Of the 13 non-responding placebo patients in RHODOS, data is available on 8, of whom 2 responded. These data show that between Baseline of RHODOS and RHODOS-OFU there were 50% of patients with "off-chart" VA in the Idebenone group and 25% in the placebo group improved to "on-chart" VA.

Patient 23 was identified as a strong confounder to the outcome in RHODOS, irrespective of his treatment assignment, and particularly for the subgroup of patients with concordant VA at Baseline presenting for treatment within 1 year of the onset of symptoms.

Since the purpose of the natural history analysis was to identify confounders and to quantify the impact that they may have had on RHODOS outcomes, an analysis of the VA outcomes for the primary endpoint in the RHODOS-OFU study, *Best VA* (main secondary endpoint in RHODOS), was conducted with and without Patient 23. These analyses are presented in Table 20 below.

Table 20. Primary RHODOS-OFU Endpoint: *Change in Best VA* (Total Efficacy Population - Observed Cases) including or excluding Patient 23

Change in Best VA	Estimated Change (95% CI) [estimated change in letters]		Estimated Difference ± SEM (95% CI) [difference in letters]	p-value
	SAN Idebenone in RHODOS	Placebo in RHODOS	SAN Idebenone vs. Placebo	
N	39	19/18 excl. P23		
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 Wk 24 Excluding P23	-0.053 (-0.176, 0.070) [+2 letters]	0.189 (0.017, 0.361) [-9 letters]	-0.242 ± 0.097 (-0.434, -0.050) [12 letters]	0.0140

These results show that the benefit on *Best VA* of treatment with idebenone during RHODOS was maintained after discontinuation of therapy (11 letters in RHODOS; 12 letters in RHODOS-OFU).

- **Retrospective studies**

Mashima et al., (2000)

This retrospective study reported the visual outcomes in patients with LHON after treatment with idebenone, vitamin B2 and vitamin C as compared with that of untreated patients with LHON.

LHON patients who had presented at the neuroophthalmology clinic in Keio University Hospital between 1980 and 1995 and had been followed for between 2 to 19 years from disease onset were selected for the study. Twenty eight patients with LHON were divided into 2 groups. The untreated group comprised 14 patients who had visited the clinic before 1990 (Group 1). Fourteen patients who received idebenone (180 mg/day) combined with vitamin B2 and vitamin C for at least one year since 1990 comprised the idebenone-treated group (Group 2). Among the untreated patients (mean age at onset 23.1 ± 8.9 years), 10 had the G11778A mutation, 2 had the G3460A mutation and 2 had the T14484C mutation. Among the 14 patients treated with idebenone (mean age at onset 23.6 ± 8.2 years), 11 had the G11778A mutation, 1 had the G3460A mutation and 2 the T14484C mutation.

The time period between onset of LHON and the initiation of treatment in patients in Group 2 who achieved visual recovery ≥ 0.3 (decimal acuity) was 5.5 months (range 2 to 9 months).

Visual function was evaluated by testing the subject's best-corrected VA and by perimetry. The authors examined the number of eyes with visual recovery ≥0.3, the interval between the onset of LHON and

the beginning of visual recovery, the interval between the onset of LHON and visual recovery to 0.3 and the interval between the beginning of medical treatment and the beginning of visual recovery in the treated subjects.

Differences in the number of eyes with visual recovery in each group were evaluated according to mutation present using Fisher Exact probability test. Differences between intervals were analyzed by Mann-Whitney U test. A level of $P < 0.05$ was considered statistically significant.

La Morgia et al. (2011) and Carelli et al. (2011)

This retrospective study was originally published as a poster (La Morgia et al., 2011) and then as a peer reviewed journal article (Carelli et al., 2011), with slightly different content and detail. Hereinafter, this cohort will be referred to as the La Morgia/Carelli cohort.

These authors reported a retrospective evaluation of the efficacy of idebenone in a cohort of LHON patients treated for at least 12 months. One hundred and three patients with LHON carrying one of the primary LHON-specific mtDNA mutations were included in the study. Forty four patients (37 males) were either treated within 1 year after the onset of VA loss in the second eye (n=38) or treated before the involvement of the second eye ("in-between-eyes"; n=6), defining the entire group as idebenone treated (IT). Thirty patients had the G11778A, eight the G3460A and six the T14484C mutation. Fifty nine non-treated (NT) patients were included in the study (40 males). Of these, 43 patients had the G11778A, 10 the G3460A and six the T14484C mutation. The groups did not differ significantly for gender, age at onset, proportion of LHON mutation type and VA for the best and worst eye evaluated at the nadir of visual loss (between 6 and 12 months after disease onset).

The idebenone dose given to patients in this cohort ranged from 270 mg/day to 675 mg/day.

VA of the best and the worst eye at the last available examination assessment was used as the primary outcome measure. Recovery of VA was considered for patients or eyes (some patients recovered vision in only one eye) with a gain of at least two lines on Snellen acuity or a change from 'off chart' to 'on chart' VA. For all patients the age of disease onset; time lapse between loss of VA in the eyes; time between disease onset and start of therapy (IT group); time between disease onset and recovery of VA; average therapy dosage (IT group); and therapy duration (IT group), were established. The interval between loss of vision in the eyes was evaluated only for the patients with asynchronous onset of symptoms, which was 56% for G11778A, 50% for G3460A and 67% for T14484C mutation. The impact of all covariates on visual recovery was assessed using a proportional hazards model. Furthermore, the interval between asynchronous disease onset in the first and the second eye in patients treated before the involvement of the second eye ('in-between-eyes'), patients treated after the involvement of the second eye and patients not treated were compared separately using the Kruskall–Wallis test followed by a post hoc Mann–Whitney U test. For all analyses, two-sided $P < 0.05$ was considered statistically significant.

- **Case reports**

Additional clinical data on the use of idebenone in LHON is available from eight published case reports (Mashima et al., 1992; Cortelli et al., 1997; Carelli et al., 1998a; Carelli et al., 1998b; Carelli et al., 2001; Barnils et al., 2007; Jancic, 2010; Sabet-Peyman et al., 2012) describing an additional 23 patients. Brief narratives of each of these publications are provided here and are also presented in Table 21.

Table 21. Overview of case reports and retrospective studies of idebenone in LHON (in chronological order)

Author Year	No. of patients	Idebenone Dose	Duration of treatment	Design	Clinical effect	Further comments
Mashima et al., 1992	1	90 mg/day	1 yr	Case report	Full remission in both eyes after 4 and 7 months respectively	G11778A mutation
Cortelli et al., 1997	1	135 mg/day 270 mg/day 405 mg/day 270 mg/day	2 days 2 days 2 months 1 year	Case report	After 4 days of idebenone treatment patient noticed improvement in strength and spasticity; complete recovery from spastic paraparesis within 6 days. Patient had stable clinical conditions for 3 months when he received 405 mg/day. Patient reported increase in clumsiness and weakness upon withdrawal from idebenone. Restart of idebenone treatment improved leg strength and spasticity which was stable for 1 year on 270 mg/day idebenone. Reversal of paraparesis by idebenone was paralleled by normalization of 31P-MRS, serum lactate and central motor conduction.	G11778A mutation Patient with "spastic paraparesis", lesions in brain MRI
Carelli et al., 1998a	6	Acute cases 135 mg/day Chronic cases 270 mg/day 360 mg/day	1 year (n=3) 1 year 1 year	Case reports as poster	3 acute cases (onset within 1 year of treatment) experienced recovery of VA and visual field. 3 chronic cases (onset over 5 years previously) had no improvement. Normalization of serum lactate (in 5 of 6 cases)	4 with G11778A, 1 with G3460A and 1 with T14484C mutations.
Carelli et al., 1998b	1	270 mg/day & Vitamin B12 (5000 IU/d)	6 months	Case report	Newly diagnosed patient (3 mo) Improvement in VA: OD 20/200→20/25, OS: 8/200→20/30 after 3 months' idebenone. Improved VA maintained 6 months after idebenone withdrawal (OD/OS: 20/20).	T14484C mutation, North African origin
Mashima et al., 2000	14	180 mg/day & Vitamin B2 (60mg/d) & Vitamin C (750 mg/day), Isopropyl uno-prostone (N=8 of 14)	≥ 1 yr	Prospective open study in 14 patients, retrospective comparison with 14 untreated LHON patients.	Number of eyes with recovery in VA ≥0.3 (decimal acuity) not statistically different between untreated and treated groups (trend for the G11778A mutation). Analysis of patients with visual recovery: significantly shorter period to onset of recovery (17.4 vs. 11.1 months, p=0.03), interval between onset of LHON and recovery was 34.4 months in untreated and 17.6 months in treated patients, p=0.01). Mean interval between the initiation of idebenone treatment and the	G11778A (N=11), G3460A (N=1) and T14484C (N=2) mutations. Interval between onset of LHON and treatment was 2-9 months
Carelli et al., 2001	2	Pat 1: 270 mg/day Pat 2: 450 mg/day 675 mg/day	11 months 4 months 3 months	Case reports	Patient 1(19 years): At start of idebenone therapy: OD: 1/50; OS: counting fingers. After 11 months on treatment: slightly worsened VA; markedly decreased intensity and frequency of myoclonic jerks, MRI lesions disappeared. Patient 2 (45 years): received steroids as first line therapy. At start of idebenone therapy (450 mg/d) both eyes were affected (OD: hand motion, OS: 3/10). Within first month on idebenone, patient reported further progression of vision loss. After 3 months therapy: improved VA in both eyes: OD: HM→1/50, OS: 3/10→1/20. Idebenone dose was increased to 675 mg/d. Within 3 months patient no longer complained of fatigue and paresthesias and reported further subjective improvement in VA: OD:	Pat 1: treatment began 10 months after onset of LHON symptoms Pat 2: treatment began 22 months after visual loss in right eye and 4 months in left eye. G11778A mutations (both patients)
Barnils et al., 2007	2	270 mg/day	1 yr	Case report	Patient 1 (30 years): bilateral vision loss at start of therapy (OD: counting fingers; OS logMAR 1): Patient received mega- dose of methylprednisolone and 270 mg/d idebenone plus multi-vitamin cocktail. After 11 months: loss of VA in OS (final VA OD: detection of hand motion; OS: finger counting). Idebenone & vitamins did not prevent visual loss in least affected eye Patient 2 (19 years): bilateral vision loss (OD: logMAR 1, OS: counting fingers). Patient received mega-dose of methylprednisolone followed by	G11778A mutations. In both patients, idebenone combined with vitamins did not prevent visual loss in the least affected eye.
Jancic, 2011	9	135 mg/day	Up to 1 yr	Case reports	There were no significant changes in VA, visual field or fundoscopic findings. 3 patients (1 with G11778A, 1 with G3460A and 1 with T14484C mutations) reported subjective improvement of VA. 1 patient (G11778A) with only 1 eye affected had no progression of visual loss in the affected eye or spreading to the other eye. Improvement in visual evoked potentials (VEP) was documented in 4 patients (1 with G11778A, 2 with G3460A and 1 with T14484C mutations). VEP recovery was transient, after medication withdrawal VEP detected amplitude and latency worsening in all cases. Author concluded that continuous administration of idebenone may stop	G11778A (N=5), G3460A (N=3) and T14484C (N=1) mutations. Patients were followed for 2 months to 3 years from disease onset

La Morgia et al., 2011; Carelli et al., 2011 **(La Morgia/Carelli)**	44	270-675 mg/day	up to 5 years	Retrospective study (comparison of 44 patients treated with idebenone within 1 year of contra- lateral onset of symptoms to 59 untreated patients)	Higher proportion of eyes/patients recovering VA in idebenone group (45.5% / 39.8%) compared to non-treated group (32.2% / 31.4%). Shorter interval between symptom onset and recovery in idebenone-treated patients (all mutations: idebenone: 17 months; untreated: 25 months; G11778A: idebenone 17 months, untreated: 28 months).	Significant association between idebenone therapy and VA recovery (p=0.031) for G11778A mutation
Sabet-Peyman et al., 2012	1	900 mg/day (plus 200 mg/d CoQ10 and i.v. 250 mg methyl prednisolone every 6 hrs for 3 days)	9 months	Case report	Patient had VA 20/200 (logMAR 1.0) in both eyes at the time of treatment start. Two months after treatment start VA improved to 20/70 (logMAR 0.55) in the right eye, the left eye remained unchanged. Thereafter, patient showed continued bilateral improvement and after 9 months VA reached 20/25 (logMAR 0.1) in both eyes. Patient also improved markedly in colour vision and visual fields.	G11778A mutation; Female patient (31 y)

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The Study RHODOS constitutes the main basis to support the efficacy and safety of idebenone in the treatment of LHON patients. It was aimed at assessing whether administration of idebenone can improve visual function in these patients. It was initially conceived as an exploratory trial to be subsequently validated in a larger confirmatory trial. Due to the difficulties in recruiting patients with this condition and after consultation with the SWAP and national agencies the study was amended to use it as a "pivotal" trial supportive of the marketing authorisation of the product. Bearing in mind these relevant features it should be highlighted that a placebo controlled study is a rare design for such a rare condition and provides the study with an additional scientific value.

The inclusion/exclusion criteria are considered reasonable taking into account the characteristics of the disease.

All 85 randomized patients were included in the Safety Populations. A total of 53 patients treated with idebenone and 29 patients treated with placebo were included in the ITT population for all VA endpoints. All 85 subjects with available data were included in other ITT analyses. The PP population included 65 patients, 41 treated with idebenone and 24 treated with placebo.

Demographic characteristics were similar for both treatment groups. As expected, mean age was around 33 years ranging from 14 to 66 years old, which represents the broad spectrum of the target population. Men were preferably recruited, with a low number of female patients (n= 8) treated with idebenone. About 80% of the recruited patients carried an mDNA mutation in which the spontaneous evolution is not expected. Mutation status was also balanced between both treatment arms, the majority presenting G11778A mutation (67%) , followed by T14484C (20%) and G3460A (12.9 %).

Having patients stratified by mutation type seems a reasonable approach since differences in disease progression can be observed for each mutation. The natural course of the disease also justifies the distinction between the "acutely ill patients" and the "chronically affected patients".

According to visual acuity characteristics at recruitment about 85% of patients suffered from an advanced vision loss (both eyes with logMAR ≥ 1.0) and almost 50% patients were off the numerical scale, counting fingers at best (logMAR ≥ 2.0). The vision seems to be still preserved only for a small group of patients. The mean duration since vision loss was 23 months and baseline VA was 1.73 logMAR. The average exposure was 192 and 197 days in the idebenone and placebo groups, respectively. A total of 93% of patients in both groups were exposed for 24 weeks.

There were more smokers and subjects with a longer history of smoking in the placebo group. Since smoking has been reported as being associated with disease penetrance in LHON it is unknown

whether, and/or to what extent smoking may affect disease progression and whether this unbalance may have an impact on the outcome of the study. Results of further analyses performed by the applicant indicate no evident influence of smoking on the targeted patient population.

Of the 85 patients randomized and treated, a small number of patients (7) discontinued the study prematurely, 3 (5.5%) on idebenone and 4 (13.3%) on placebo. This doesn't trigger any concern.

Efficacy data and additional analyses

The primary endpoint – Best Recovery - did not reach statistical significance (p=0.291) and the difference in VA between treatment arms was not clinical relevant (3 letters in favour of idebenone). In the subgroup of patients with mutations G11778A and G3460 and a low chance of a spontaneous recovery, a 4 letter clinically non- relevant difference between treatment arms was observed (p=0.187).

The key secondary endpoint – Best Visual Acuity is regarded of higher clinical relevance. For this endpoint, the effect shown was non-statistically significant and non-clinically relevant effect (logMAR -0.120, 6 letter difference) ; the p-value was 0.078.

Focusing on the subgroups with mutations G11778A and G3460, a bigger effect size, but still not clinically relevant, was observed (8 letter difference, p=0.037). On the contrary, a consistent lack of effect in subjects with mutation T14484C (those with the largest potential for a spontaneous improvement in VA) could suggest that this subset of patients are not benefiting from treatment with idebenone. Further considerations to the analyses performed on the efficacy data collected in the pivotal trial are given below in "Indication" section.

Three retrospective cohort studies (Carelli 2011, Mashima 200 and Orssaud 2012) involving 14, 44 and 63 patients were identified as providing the most relevant and reliable efficacy data. Orssaud's study results suggest a beneficial effect of idebenobe. In this study patients were treated with idebenone 270 mg/day for 2 years. Around 30% of patients treated with idebenone showed VA recovery from mean logMAR 1.461 for both eyes to logMAR 0.673 at the end of treatment. In addition, 68% of patients who improved vision carried G11778A mutation.

The study by Carelli et al (2011) is considered by the applicant as the most helpful despite being open-label and retrospective (n=44) since it included the largest sample of patients and has a control group of comparison of 59 untreated patients. Patients were enrolled within 1 year of symptom onset and received idebenone 270-675 mg/day for 5 years. Mashima's study also included a comparative arm of patients without treatment but the sample size was smaller (n=14). Also patients were enrolled within 1 year since symptom onset. Patients were given idebenone 180 mg/day plus vitamine B2 and C for 1 year. Patient characteristic at baseline were similar with respect to average age at onset (23 years for Mishima's study and 26 years for Carelli's study) and patients with G11778A mutation (79% and 68% respectively).

Responder rate is considered a meaningful measure of the clinical benefit of a given drug. The Applicant has provided responder rates for Mashima's and Carelli's studies compared to those for RHODOS study. Although different responder definitions were used between studies it can be considered globally similar and clinically relevant in all cases (recovery in VA>0.3 logMAR in Mishima's study and improvement in VA by 2 lines or from off-chart to on-chart in Carelli's study). In both studies there were more responders in the group of patients on idebenone than in those on placebo (Carelli's 42.9% versus 28.6%; Mashima's 45.5% versus 32.2%). These percentages were higher than those observed in the study RHODOS (31.6% versus 0%) where the definition of responder was improvement of VA by>10 letters or from off-chart to on-chart. It cannot be determined whether the discrepancy between untreated patients from literature and RHODOS study (placebo) is due to the

small numbers, the different follow-up of the subjects, and the intrinsic variability of the course of the disease or any other factors.

Results of Mashima's and Carelli's studies show a similar positive trend of idebenone effect in LHON patients.

It must be recognised that using data from literature has its limitations derived from the publication bias. and therefore didn't publish those results.

- **Indication**

Post hoc analyses showed effects on VA in the subgroup of patients with discordant VA at baseline (n=30), i.e. in subjects who were in a more acute phase of the disease and at risk of further vision loss in the eye with residual VA. A mean of 14 and 21 letter difference (including the semi-quantitative assignments of VA for patients off chart) in favour of idebenone was observed in the primary and key secondary analyses, respectively (p=0.011 and 0.003). This is a large difference although it doesn't mean that the patient gains a "good" VA. While further progression of vision loss may be reduced or halted for some patients, others may be able to read a line or two on the chart instead of counting fingers or seeing hand movements from a close distance.

According to the identified effect, idebenone could prevent vision loss in the LHON patients with discordant visual acuity. A relevant concern is how this subgroup, which was defined post hoc, is translated into the real practice. The CHMP hadreservations on how the operational definition of "patients with discordant visual acuity" would allow the identification of the group of patients to be treated in the clinical setting.

Further analyses run by the applicant indicated that a population "at risk" of disease progression or those who may be able to recover visual acuity if treated early might constitute the group mostly benefiting from idebenone treatment. ("Patients with Leber's Hereditary Optic Neuropathy (LHON) due to G11778A or G3460A mitochondrial DNA mutations presenting for treatment within one year of onset of symptoms").

This proposal is based on the results from 24 patients (11 with discordant VA and 13 with concordant VA). One patient was considered as outlier and excluded from the analysis. The Applicant identified patient 23 (mutation G 11778A), a patient that spontaneously gained VA before start of study. Although the chance of visual recovery for this mutation is described to be the lowest in comparison with the other two common mutations, it has been reported to occur. Since the patient regained full vision with an improvement starting before screening and randomisation, it seems highly likely that this subject recovered spontaneously.

The conducted analysis in the subgroup of patients carrying G11778A or G3460A mutations and treated within one year of onset of symptoms in RHODOS study show a difference from baseline to Week 24 of + 23 letters (p = 0.007) in favour of idebenone. The CHMP considered these results as not sufficiently reliable since they are based on a post hoc analysis therefor subject to methodological bias.

In order to address these concerns a new target population has been defined by the Applicant, corresponding to patients presenting for treatment within one year of of onset of symptoms, regardless of the mutation type. The revised target population, was a pre-specified sub-group analysis in the RHODOS protocol.

Whilst patients carrying the T14484C mutation were previously excluded to eliminate the potentially confounding effect of the high rate of spontaneous VA recovery reported in these patients (Yu-Wai-Man et al., 2009; Fraser et al., 2010), it can be seen that the re-inclusion of these patients reduces treatment effect size from 23 letter (for Onset $\leqslant$ 1 y; G11778A or G3460A*) to 17 letters for the Best VA endpoint in the revised target Population (Onset $\leqslant$ 1 y; ITT*). These results also show consistency

with other related outcomes (such as the response by individual eyes count) and, in general, with respect to all submitted results.

Mechanistically, it would be more plausible to treat patients with a recent onset of the disease in order to obtain an effect (accelerating or promoting visual recovery). This approach is also supported by some reported cases/cohorts available in the literature.

A number of published data have been provided by the applicant to support the effect of idebenone on LHON patients. Overall 143 patients treated with a broad range of idebenone dose (90-900 mg/day) are presented. The majority of patients (n=126) received between 270 and 675 mg/day, a lower dose than the one given in the RHODOS study. Seven out of the 10 studies met the revised definition of the target population as proposed by the applicant (enrolled within 1 year from onset of symptoms carrying any of the three primary mtDNA mutations).

Based on the RHODOS data the applicant presented the relationship between time from onset of symptoms and effect size which shows that the shorter the time since diagnosis and treatment the larger effect size is observed. This would support the use of idebenone in early stages of the disease as proposed by the applicant.

The same cut off of 'one year since the onset of symptoms' for treatment initiation was indicated by the expert panel consulted by the CHMP. (see "additional expert consultation" section for further details).

In terms of whether patients presenting T14484C mutation should be included in the target indication the expert panel recommended their inclusion. This recommendation takes into consideration the clinical practice experience, practical considerations and the fact that spontaneous recovery does not occur in 30-50% of these individuals.

Based on all above evidence the CHMP could agree that the target population that would mostly benefit from treatment consists of: patients with the disease onset within 1 year regardless of the mutation type.

- **Confounders**

CHMP had raised concerns on the reliability of the data due to the potential confounders. The applicant provided additional analyses addressing the influence of other factors than idebenone on the effect observed in LHON patients. They primarily refered to the natural history of the disease itself, the possibility of spontaneous recovery of VA and the potential influence of differences in the baseline characteristics of the studied population on the outcome.

Spontaneous recovery and natural course of disease

The possibility of recording a spontaneous recovery effect (and therefore of measuring a supposed effect) is a matter of concern. In this sense, and differently from T14484C mitochondrial DNA mutation, the spontaneous remission in patients carrying the G11778A and G3460A mutations is less likely. Additionally, the phase with higher probability of spontaneous recovery of visual acuity is believed to occur within the 2-5 year period after onset of symptoms.

Nevertheless, spontaneous recovery of VA has also been described and it mainly depends on the DNA mutation. Data from publications show that G11778A is the most prevalent mutation in Europe and the one less likely to stabilise/recover spontaneously (between 4% and 23% of patients depending on the studies) compared to G3460A (between 15% and 25% depending on the studies) and T14484C mutation that is known to be the one with the highest probability of spontaneous improvement of VA (between 37% and 71% depending on the studies). In the RHODOS study, patient 23 recovered VA spontaneously prior randomisation until normalisation of VA. This patient had a very rapid recovery

pattern and it was excluded from the ITT population. Even though the exclusion of patient 23 from the efficacy analyses may be considered acceptable, given the small number of patients and the major impact that the inclusion of patient 23 had on the results of the efficacy analyses the CHMP is concerned on the potential effects of "spontaneous recovery" of any individual patients on the observed results.

In order to estimate the potential effect of other spontaneous improvements of VA in LHON patients the Applicant has assessed all patients with significant improvement of VA in the RHODOS study (n=6). In all cases recovery pattern was slower than the one of patient 23. Only 1 carried the T14484C mutation while the rest carried the other two mutations less likely to be associated to spontaneous recovery. No improvements in VA occurred in patients on placebo., Differently from what is described as a spontaneous recovery a stabilisation pattern of the vision (i.e. preservation of vision function) has been measured in idebenone patients, and not in placebo group, which followed the expected progression of vision loss according the natural course of the disease.

This different behaviour between treatment groups has also been observed when eyes (and not patients) are analysed. These results have certain limitations given that every single eye cannot be strictly considered independent from its fellow eye.

The Applicant has also provided the responder rate for patients with G11778A mutation, the mutation less likely to present spontaneous recovery (Mishima's 36.4% versus 10%; Carelli's 46.7% versus 23.3% and RHODOS 21.4% versus 0%), showing even larger differences versus placebo than in the whole population.

Baseline characteristics

It has been widely described that LHON starts with involvement of one eye and there seems to be agreement that the second eye is involved shortly. Data from some publications (Newman et al, Riordan-Evan et al and Fraser et al) show that more than 97% of patients develop second eye involvement within one year. These data indicate progressive deterioration of VA over time, most patients suffering devastating and permanent vision loss.

When compared, the selected subgroup of patients of RHODOS study in whom the efficacy relies on – the (Target Population) presents similar visual acuity at recruitment to that reported in untreated patients (historical controls). This applies to both idebenone and placebo patients. A comparable course of the condition in both groups (towards the vision loss) would then be expected.

A further analysis of the characteristics of patients at baseline (age at recruitment, age at onset of the condition, mutations, smoking status) suggests that they have not been preferentially selected and a different evolution for idebenone and placebo patients would not be predictable.

- **Maintenance of effect / adaptive changes to the disease**

A group of patients of RHODOS study (58 out of the 82 patients originally recruited) were assessed after finalising the study (Follow up study: RHODOS-OFU). Five out of the 54 patients had been treated in this period with idebenone.

For the patients in the Total Efficacy Population (n = 58 patients) in RHODOS-OFU, the difference between treatment groups was logMAR -0.175, equivalent to 8 letters favouring idebenone (p=0.0844). Best VA was measured at the RHODOS follow up visit which took place at a median time of 30 months after Week 24. It resulted in an 8-letter difference (logMAR -0.173) between treatment groups at the RHODOS follow up visit (p=0.0845).

In the subgroup of patients (n=14 previously idebenone, n=6 previously placebo) with onset of symptoms of ≤1 year (targeted indication) at Baseline of RHODOS study and mutations G11778A or

G3460A the mean treatment difference at Week 24 was logMAR -0.249, equivalent to 12 letters favouring idebenone (p=0.3180). By the time of the RHODOS follow up visit Best VA showed a treatment difference for the change from Baseline to the RHODOS follow up of logMAR -0.203 (corresponding to 10 letters, p=0.4043).

The treatment differences for the analysis of Change in Best VA excluding Patient 23 based on medical grounds, favoured idebenone at Week 24 (logMAR -0.242, corresponding to a 12-letter difference) and at the RHODOS follow up (logMAR -0.230, corresponding to an 11-letter difference).

Long-term follow-up data were available for 5 of the 7 patients who had improved from “off-chart” vision at Baseline of in RHODOS study to “on-chart” vision at the Week 24 of the RHODOS study. These 5 patients still had “on-chart” vision at RHODOS follow up.

The subset of patients with onset of symptoms of ≤ 1 year (the intended indication) follows a similar difference to that observed in the 24-week RHODOS period. This finding might provide some support to the potential role of idebenone in LHON.

Remarkablye, however, there is a trend to improvement in both arms from 24 week visit on. The Applicant has argued medical reasons (related to the learning of patients to cope with the central scotoma by using peripheral vision). Even though the adaptive change to disease can be considered a plausible explanation for the trend of improvement such trend cannot be confirmed since no additional data corresponding to any data points between week 24 and week 132 are available.

Moreover it is questioned whether adaptive changes to disease contributed to the effect size observed during the RHODOS study in the target population.

Whether other factors, such as the reductionof the sample size (only 58 out of 85 patients were included in the follow-up visit), the use of off-label idebenone in 5/58 subjects or the possible higher retention of those more favourable cases could have impact on the final outcome should also be taken into consideration. Therefore, and although in principle no signals of spontaneous recovery are observed firm conclusions cannot be drawn.

- **Need for additional confirmatory data**

Given that the main evidence of the effect of idebenone in LHON is based on the data collected in 28 patients (19 treated with idebenone) which represents a subset of the population enrolled in the pivotal trial, confirmatory data is needed in order to validate these observations. Moreover it would give an opportunity for collection of long-term efficacy and safety. However, the applicant estimated that a placebo-controlled confirmatory study involving 110 patients in the target population (onset of disease within 1 year; all 3 mutations) and followed-up for two years would require up to 7 years to have available results. The indication for which the product is intended is so rare that the CHMP acknowledged that the feasibility of a placebo-controlled study in the newly diagnosed patients is questionable. Such study would become even more unfeasible to conduct once the product is on the market.

Instead, a Product Exposure Registry, in which patients treated with idebenone could be periodically assessed for efficacy was proposed by the applicant in an attempt to provide additional long term safety and efficacy data under the conditions of routine clinical practice. Such registry would be planned to run for 5 years with a minimum of one year per patient. In co-operation with the European clinical research network EVICR.net a historical control group would be included. VA measurements would be evaluated as changes from baseline with endpoints including at least the Best Visual Acuity and Visual Acuity in Both Eyes. Supplementary information on OCT examination would add additional efficacy support. Periodical measurements of visual function (VA and OCT measures) following the

scheduled recommendation of the administration of the product would be considered of help in order to sustain the efficacy of idebenone.

Additional expert consultation

The consultation of an ad-hoc expert group was requested by the CHMP in order to provide advice on the reliability of the results and the biological plausibility of the effect of the drug in the identified sub-population of LHON patients that seemed mostly to benefit from idebenone treatment: patients presenting for treatment within one year of onset of symptoms, regardless the mitochondrial mutation type.

The expert panel made the following recommendations:

- Based on the clinical practice experience and from a practical perspective, the expert panel would recommend the inclusion of patients with mutation T14484C in the target population. The expert panel did not see any reasons for not allowing patients with T14484C mutation to have access to a possible idebenone treatment given that spontaneous recovery does not occur in 30-50% of these individuals.
- The cut off of 'one year since the onset of symptoms' was found to be a reasonable time frame within which idebenone treatment should be initiated as this would be an approximate timeframe within which the retinal ganglion cells might still be recoverable. However each eye should be treated separately in terms of treatment eligibility. In patients having both eyes affected the one year cut off should be counted from the onset of the disease in the latest affected eye.
- It is important to note, however, that the expert panel felt that having a cut off of one year should not be regarded as exact and would be very difficult to justify to an individual with a 13 month history of symptoms. The panel felt that there might be other structural and functional measures that could be used to predict whether treatment might benefit an individual such as OCT measurements (structural measure) and pattern ERG investigations (function predictor). These might be especially useful in the group of individuals with more than 12 months of symptoms.
- From a strictly clinical perspective an improvement in VA of +17 letters can be considered functionally relevant and the expert panel felt that the presented results were promising. However, the panel felt that there are additional objective (and subjective ways) of measuring functional improvement that could have been included such as visual field analysis, using one of the newer methods of measuring central scotomas in poor fixators, Pattern ERGs, colour vision assessment and Quality of life questionnaires. This additional data might help to distinguish a treatment effect more convincingly.
- The expert panel felt that as the participant numbers were so small in the study they could not exclude that the clinical effect seen at the end of the treatment period (week 24) would be, at least in part, the result of spontaneous regression of the disease. The powerful effect of inclusion or exclusion of patient 23 on the final analysis results could be an indicator in this sense.
- Due to insufficient data clearly characterising Idebenone's mechanism of action in LHON, the expert panel were not able to indicate either way whether it is biologically plausible that Idebenone would have an effect in the overall LHON population. The expert panel felt that the animal data from pre-clincal studies shed some doubt on whether the proposed dose for Idebenone would reach measurable concentrations in the vitreous to be causing a biological effect and, as it appears to be cleared from the mouse vitreous within 30 minutes, the panel also had doubts about the proposed tds treatment regime.

- Overall the expert panel felt that, whilst a positive trend was observed, due to the very small sample size included in the subgroup analyses the results were not reliable enough for the expert panel to have confidence in their interpretation.
- There is a paucity in clinical experience on longer term evolution of the disease since patients are not usually followed up after they reach the chronic, stable phase. In addition publicly available data on long term evolution of LHON is not available. Therefore, the expert panel felt that they collectively lacked the absolute knowledge to indicate reasons that would truly explain the observed trend in VA improvement in RHODOS follow up study. There is, however, evidence that some individuals do spontaneously improve vision over years and fenestration of the central scotoma can occur which may allow better use of 'minimally off-centre' vision. Furthermore adaptation to the central scotoma and use of peripheral vision may offer explanations as to why improvements are seen.
- The expert panel felt that the presentation of a 'parallel' trend of VA improvement was misleading since it is based on the assumption that the long term evolution of LHON is a linear one. More data collection points between week 24 (RHODOS) to week 132 (RHODOS follow up study) would be needed to confirm the "parallel" trend of VA improvement. From the data given, there are no reasons to believe that at an earlier or later time point all patients regardless of whether they received Idebenone or placebo would not reach the same level of VA improvement.

2.5.4. Conclusions on the clinical efficacy

The single pivotal trial failed to show a clinically relevant and statistically significant effect of idebenone in the whole population of Leber's hereditary optic neuropathy. This statement applies for both primary and main secondary end point.

The efficacy has been shown for the main secondary end point, which is considered of highest clinical relevance, on the results observed in patients with the onset of disease within one year, regardless the mitochondrial mutation type (target population). This represents a small subgroup of patients 28 patients (19 treated with idebenone).

The reliability of the efficacy results of idebenone in the proposed target population is questionable. Given the limited size of such subgroup, the possibility that the clinical effect seen could be due to a spontaneous regression or adaptive change to the disease cannot be ruled out. The powerful effect of inclusion or exclusion of patient 23 on the results of the efficacy analysis could be an indicator to which extent such confounder (e.g. spontaneous regression) has on the results obtained in the target population.

In addition, the non-specific mechanism of action of idebenone does not support sufficiently the biological plausibility of idebenone effect in the overall LHON population.

The maintenance of effect has not been conclusively demonstrated. Even though the treatment effect difference between the idebenone and placebo arms has been almost the same one year after the treatment was stopped, the trend to positive evolution of patients in both arms was seen. This finding could be at least in part attributed to patients' ability to learn to use extrafoveal vision in patients with central scotoma (adaptive changes to disease). Whether other factors, such as the reductionof the sample size (only 58 out of 85 patients were included in the follow-up visit), the use of off-label idebenone in 5/58 subjects or the possible higher retention of those more favourable cases could have impact on the final outcome should also be taken into consideration. Therefore, and although in principle no signals of spontaneous recovery are observed firm conclusions cannot be drawn.

2.6. Clinical safety

This application for Raxone in LHON has been submitted under the legal basis of Art. 10(3), with Mnesis as the reference medicinal product. Efficacy and safety data are available from one double-blind, randomized, placebo-controlled study in LHON. Clinical data collected from the clinical development program for Friedreich's ataxia (FRDA) (another rare mitochondrial disease), provide additional safety information and are therefore considered and discussed in this document. In summary, the following clinical data are presented:

•One completed double-blind study in LHON: RHODOS (SNT-II-003).

•One completed Observational Follow-Up Study in patients completing RHODOS (SNT-II-003 OFU)

•Three completed double-blind studies in FRDA: NICOSIA (SNT-II-002), IONIA (SNT-III-002) and MICONOS (SNT-III-001). Subjects completing the MICONOS and IONIA studies were able to enroll into the corresponding open-label, long-term extension trial. The IONIA extension is complete and the MICONOS extension is ongoing.

• Four completed Phase I studies in healthy volunteers: SNT-I-001, SNT-I-002, SNT-I-003, and SNT-I-004.

The safety database of the RHODOS Study forms the basis for the safety assessment Raxone 900 mg/day in the treatment of patients with Leber's Hereditary Optic Neuropathy (LHON). Safety data from FRDA studies and phase I studies in healthy volunteers are also presented. Regarding all these studies, three different populations are included in the safety database (i.e. LHON patients, FRDA patients and healthy volunteers). The differences in condition, range of age and exposure to the drug result in different populations and therefore, it seems reasonable to analyse them separately.

The Phase I studies have been included but they are 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). Consequently, the assessment of the safety data relies on the pivotal phase III trial (RHODOS) and data from the FRDA studies is considered supportive for the safety evaluation.

Patient exposure

LHON

Safety data are available from one double-blind, randomized, placebo-controlled study in LHON (RHODOS [SNT-II-003]). A limited number of patients with LHON (55 subjects) have been exposed to idebenone for a limited time (study length 6 months, mean exposure time of 192 days). 51 subjects were exposed for 24 weeks.

RHODOS (SNT-II-003 OFU) observational follow-up study in patients completing RHODOS study. The patients were off-treatment and only 5 patients received idebenone "off label".

FRDA

The proposed dose recommendation for LHON (900 mg/day, 2 tablets 3 times a day) is comparable to the doses used (180-2250 mg/day) in studies of Friedreich's ataxia (FRDA - another rare, mitochondrial disease). Therefore, safety data from this program are also considered and discussed. This program includes three completed double-blind studies in FRDA: NICOSIA (SNT-II-002), IONIA (SNT-III-002) and MICONOS (SNT-III-001). Subjects completing the MICONOS and IONIA studies were able to enrol into the corresponding open-label, long-term extension trial. The IONIA extension is complete and the MICONOS extension is ongoing.

A limited number of subjects with FRDA have been exposed to Idebenone (in total 256 subjects, 69 subjects 180/360 mg/day, 92 subjects 450/900 mg/day and 95 subjects 1350/2250 mg/day) and 94

have received placebo in randomized, double-blind studies. 160 subjects were exposed for 12 months. Furthermore, patients with FRDA have been followed for up to 382 days in an open-labelled study.

LHON and FRDA

Overall, safety data are available for 311 subjects treated with idebenone and 124 treated with placebo. Of the idebenone-treated subjects, 242 have received a dose ≥900 mg/day or equivalent (900 mg/day is the dose proposed for use in subjects with LHON). Nevertheless, regarding the main clinical trial (RHODOS study), a total of 85 subjects were enrolled and randomized in a 2:1 ratio for 24 weeks, with 55 receiving 900 mg/day idebenone and 30 receiving placebo. From a demographic point of view, the studied population (both male and female subjects, aged between 8 and 70 years, mostly of Caucasian/white race) is considered representative of the population suffering from LHON. However, although it is known that Leber's Hereditary Optic Neuropathy is an orphan disease, the low patient exposure to idebenone (55 patients with LHON) provides limited safety data in the target population and therefore this is considered a study limitation. FRDA studies only provide additional safety data for the evaluation of the currently submitted application.

Post marketing exposure

Since 1986, idebenone has also been marketed by Takeda in several countries for the treatment of degenerative and vascular cognitive disorders, including Alzheimer disease. Following the marketing authorization granted by the Swiss Health Authority in 2004, Periodic Safety Update Reports (PSURs) have been prepared by Takeda on a yearly basis. Santhera also receives these PSURs and submits these data for Santhera drug Catena, which approved for FRDA in Canada. The patients' population exposed to idebenone from 1-Apr-2004 to 31-Mar-2007 is estimated by Takeda in approx. 68000 patients-years.

Adverse events

In the RHODOS study, the majority of subjects had at least one AE (89% for idebenone and 87% for placebo), with a similar incidence on idebenone and placebo.

In each FRDA study, the majority of subjects had at least one AE (over 90% for all idebenone doses combined and over 80% for placebo).

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

Table 22 summarizes all the common AEs reported in ≥5% of subjects with LHON or FRDA receiving idebenone or placebo in the double-blind studies.

Table 22. Common AEs reported in double-blind studies

	LHON		**FRDA**		
N (%) subjects	**Idebenone 900 mg/day (N=55)**	**Placebo (N=30)**	**Idebenone (all doses combined) (N=256)**	**Placebo (N=94)**	**IONIA Extension** **Idebenone 1350/2250 mg/day (N=68)**
Cardiac disorders					
Left ventricular hypertrophy	4 (7.3)	0	0	0	
Gastrointestinal disorders					
Abdominal Pain	0	0	15 (5.9)	10 (10.6)	

Abdominal Pain Upper	3 (5.5)	3 (10.0)	24 (9.4)	7 (7.4)	13 (19.1)
Constipation	2 (3.6)	3 (10.0)	6 (2.3)	4 (4.3)	
Diarrhea	5 (9.1)	3 (10.0)	48 (18.8)	11 (11.7)	11 (16.2)
Dyspepsia	1 (1.8)	0	13 (5.1)	4 (4.3)	
Flatulence	0	2 (6.7)	3 (1.2)	3 (3.2)	
Gastroesophageal reflux disease					6 (8.8)
Nausea	1 (1.8)	0	41 (16.0)	15 (16.0)	
Toothache	0	0	14 (5.5)	3 (3.2)	
Vomiting	4 (7.3)	2 (6.7)	27 (10.5)	6 (6.4)	11 (16.2)
General disorders and administration site conditions					
Asthenia					4 (5.9)
Fatigue	1 (1.8)	1 (3.3)	19 (7.4)	8 (8.5)	12 (17.6)
Pain					9 (13.2)
Pyrexia	1 (1.8)	0	14 (5.5)	6 (6.4)	14 (20.6)

Infections and infestations					
Ear infection					6(8.8)
Gastroenteritis	1 (1.8)	2 (6.7)	17 (6.6)	4 (4.3)	
Influenza	6 (10.9)	3 (10.0)	23 (9.0)	7 (7.4)	11 (16.2)
Nasopharyngitis	14 (25.5)	5 (16.7)	73 (28.5)	21 (22.3)	12 (17.6)
Pneumonia					4 (5.9)
Rhinitis	1 (1.8)	0	5 (2.0)	5 (5.3)	
Sinusitis	1 (1.8)	2 (6.7)	9 (3.5)	4 (4.3)	8 (11.8)
Upper Respiratory Tract Infection	0	0	31 (12.1)	15 (16.0)	18 (26.5)
Viral infection					5 (7.4)
Injury, poisoning and procedural complications					
Fall	1 (1.8)	1 (3.3)	23 (9.0)	8 (8.5)	13 (19.1)
Joint sprain					5 (7.4)
Skin laceration					4 (5.9)
Investigations					
Alanine aminotransferase increased	1 (1.8)	3 (10.0)	3 (1.2)	0	
Blood cholesterol increased	0	2 (6.7)	0	0	
Blood creatine phosphokinase increased	1 (1.8)	2 (6.7)	2 (0.8)	2 (2.1)	
Blood triglycerides increased	6 (10.9)	3 (10.0)	0	0	
Gamma-glutamyltransferase increased	0	5 (16.7)	4 (1.6)	1 (1.1)	

Musculoskeletal and connective tissue disorders					
Arthralgia	0	2 (6.7)	13 (5.1)	4 (4.3)	7 (10.3)
Back pain	4 (7.3)	2 (6.7)	27 (10.5)	7 (7.4)	10 (14.7)
Muscle spasms	0	0	12 (4.7)	7 (7.4)	8 (11.8)
Myalgia	0	0	14 (5.5)	5 (5.3)	
Neck pain					4 (5.9)
Pain in extremity	1 (1.8)	0	22 (8.6)	6 (6.4)	12 (17.6)
Scoliosis					5 (7.4)
Nervous system disorders					
Dizziness	3 (5.5)	0	15 (5.9)	5 (5.3)	10 (14.7)
Headache	13 (23.6)	6 (20.0)	85 (33.2)	36 (38.3)	21 (30.9)
Psychiatric disorders					
Anxiety	0	0	14 (5.5)	5 (5.3)	
Insomnia					7 (10.3)
Renal and Urinary Disorders					
Chromaturia					7 (10.3)
Reproductive system and breast disorders					
Dysmenorrhea	0	0	4 (1.6)	6 (6.4)	5 (7.4)
Respiratory thoracic and mediastinal disorders					
Cough	6 (10.9)	0	7 (7.4)	23 (9.0)	6 (8.8)
Dyspnea					5 (7.4)
Oropharyngeal pain	5 (9.1)	3 (10.0)	17 (6.6)	7 (7.4)	
Pharyngolaryngeal pain					12 (17.6)
Skin and subcutaneous tissue disorders					
Pruritus generalized	1 (1.8)	2 (6.7)	0	0	
Rash	2 (3.6)	2 (6.7)	6 (2.3)	3 (3.2)	4 (5.9)

Overall, the incidence of AEs and treatment related AEs were low and similar between idebenone and placebo groups. The majority of these AEs were mild or moderate in intensity.

In the **RHODOS study**, the most common AEs reported in the treatment group were nasopharyngitis (25.5%), headache (23.6%), and influenza, blood triglycerides increased and cough (10.9% each). This incidence of AEs was also observed with a similar frequency in the placebo group.

Two subjects receiving idebenone experienced severe AEs, one 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 (see Laboratory findings section).

Table 23. Treatment related AEs reported in RHODOS study

N (%) subjects	Idebenone 900 mg/day (N=55)	Placebo (N=30)	All Subjects (N=85)
Cardiac disorders			
Left ventricular hypertrophy	1 (1.8)	0	1 (1.2)
Wolff-Parkinson-White Syndrome	1 (1.8)	0	1 (1.2)
Investigations			
Alanine aminotransferase increased	0	1 (3.3)	1 (1.2)
Blood triglycerides increased	1 (1.8)	1 (3.3)	2 (2.4)
Liver function tests abnormal	1 (1.8)	0	1 (1.2)

With respect to the treatment related AEs, 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, Wolff-Parkinson-White syndrome, and liver function tests abnormal. Of note, the incidence of left ventricular hypertrophy (LVH) was 7.3% in the idebenone group versus 0.0% in the placebo group, although only one case was related to the treatment.

In addition, 16 additional cases suggestive of LVH were also reported. At the CHMP's request the applicant has made a revision of the ECG tracings (n = 167) from 85 LHON patients involved in RHODOS study. In a number of patients (5 of 30 patients on placebo, 16,6%; and 12 of 55 patients on idebenone, 21,8%) ECG abnormalities were already recorded at the pre-treatment study visit. During the study 9,1% idebenone patients and 13,3% placebo patients developed ECG signs for LVH. The applicant has documented the reported incidence of cardiac involvement on LHON patients in the literature, and although no routine echocardiographic cardiac examination has been performed, overall these findings do not suggest a new cardiac safety signal with respect to the clinical use of Raxone.

In **FRDA studies**, the most common AEs reported in all three double-blind studies (NICOSIA, IONIA and MICONOS) were headache, diarrhea and nausea. The incidence of these events was generally similar between idebenone and placebo groups.

The treatment-related AEs reported with a higher incidence in the treatment group were: headache (15.6%) and diarrhea (12-5%).

Apparently, no dose-relationship can be established in idebenone groups. However, the low number of patients per group precludes drawing any valid conclusion.

When analysing the overall common AEs incidence in the RHODOS, NICOSIA, IONIA and MICONOS studies the following AEs were noted at a higher incidence in the subjects receiving idebenone compared to subjects receiving placebo: diarrhea (not increased incidence in RHODOS study), dyspepsia, vomiting, nasopharyngitis, back pain, pain in extremity, dizziness and cough.

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

No statistical difference was observed in the distribution of the AEs of interest between idebenone and placebo treated patients. This analysis does not rule out any relationship.

However, no cases of nasopharyngitis, back pain, pain in extremity or cough have been reported from post marketing experience to date, and only single SAEs (nasopharyngitis (1), back pain (1), pain in

extremity (1)), have been collected during clinical trials thus not supporting the relatedness of these events to idebenone. The pharmacodynamic effect of Raxone and the pre-clinical studies does not indicate a potential relationship to these AEs.

At the CHMP's request the applicant has further assessed the incidence of the AEs. The analysis indicates that of the AEs of interest only mild to moderate diarrhoea may be related to the idebenone treatment.

Bronchitis was noted at a higher incidence in the active treatment group in the MICONOS study. This AE has been analysed by the Applicant in all studies, separately and when combining the studies and no difference was observed between the idebenone and placebo groups, with respect to bronchitis or upper and lower respiratory tract infections.

Eye disorders were more common in the subjects receiving idebenone (7.3 % and 5.5 %) compared to subjects receiving placebo (3.3% and 5.3 %) in the RHODOS study and the FRDA studies, respectively. The applicant has analysed this finding in more detail and the provided analyses do not suggest that treatment with idebenone is related to the development of eye disorders.

It is noted that Chromaturia was reported in the IONIA study, and in the IONIA extension study (10.3%), at a higher incidence in the subjects receiving idebenone compared to subjects receiving placebo. This is explained by metabolites of idebenone that are coloured and may cause chromaturia, i.e. a reddish brown discoloration of the urine.

Post marketing rash, pruritus and face swelling were reported by a 17-year-old male consumer treated with idebenone 2250 mg/day. Allergic reactions are listed in the Canadian Product Monograph.

The post marketing AEs seems in line with the AEs noted in the clinical studies.

Serious adverse event / deaths / other significant events

- **Deaths**

No deaths occurred in the RHODOS study and no deaths occurred during the clinical program for FDRA.

- **Other serious adverse events**

In the RHODOS Study, there was one SAE (infected atheroma on left eyebrow) in idebenone group, not related to active treatment.

In the FRDA studies most of the SAEs and discontinuations due to AEs were unrelated to study drug and attributed to the underlying disease/pre-existing condition. Cardiac disorders such as cardiomyopathy, tachycardia, arterial fibrillation are common in Friedreich's ataxia, and from the narratives of the reported cardiac SAEs underlying disease/pre-existing condition seems to be the most plausibly explanation for these events.

Hyperthyroidism of unknown causes was reported in a 12 year-old male with FRDA (1350 mg/day idebenone, 3 tablets tid) in the IONIA extension study. According to laboratory work-up performed, the subject had a positive antinuclear antibodies (ANA) test, elevated anti-Jo-1 antibody, elevated thyroid-stimulating immunoglobulins, and increased thyroid parameters (T3 and T4 total, T3 uptake and T4 free). The central portion of the thyroid isthmus was resected and according to pathology report, the final diagnosis was: thyroid gland with focal lymphocytic thyroiditis and cystically dilated follicles containing scalloped colloid suggestive of hyperfunction.

Renal tubular necrosis of unknown causes was reported as a SAE in a 42-year-old Caucasian female with FRDA since 1980 on 2250 mg/day idebenone in the MICONOS study. The subject was asymptomatic but was hospitalized for exploration of proteinuria associated with previously observed

increased creatinemia. During hospitalization, renal ultrasound was performed. The results showed kidneys of normal size, without dilatation of pyelocaliceal cavity. However, a renal biopsy revealed acute tubular necrosis. Laboratory test results showed a creatinine level at 86 µmol/l (normal range: < 85.0) and urea level at 5.2 mmol/l (normal range from 3.33 to 8.3). Day 363, the last day of treatment the serum creatinine level was 96.4 µmol/L. Creatinine levels had decreased to 85.7 µmol/l by 4 Nov 2008 (Day 391).
The Applicant has analysed and presented data on kidney function and urinary parameters, from the individual studies and combined (see Laboratory findings section).

Severe ITP was reported study Day 75 in an 8-year-old Caucasian female (1350 mg/day idebenone), with FRDA since Oct 2004, in the IONIA study (SAE). Neutropenia was also reported as an AE in the same subject during the same time period. The SAEs resolved following treatment. Idebenone was temporarily suspended on Day 79 and restarted on Day 90 for the subject. The subject had a medical history of ITP, with the original diagnosis in 2001 and a recurrence of thrombocytopenia confirmed by bone biopsy in 2005. The event was not considered related to idebenone by the Investigator, this seems reasonable according to the CHMP.

Post marketing experience identified a SAE in a 40-year old male subject with FRDA with fulminant hepatitis and multi-organ failure. The events occurred more than 4 years after initiation of therapy with idebenone. The reporter identified other possible causes such as viral hepatitis, septic shock and cardiogenic shock. Elevated liver enzymes (ALT at 319, AST at 274; units not provided) in a 25-year old male with FRDA was also reported and classified as SAEs. In addition, one subject discontinued the RHODOS study due to elevation of hepatic enzymes. Although the role of idebenone cannot be rule out concomitant medication and comorbidities present in these patients could also explain at least two of the three cases (see laboratory findings section)

A 14-year old male with FRDA-related hypertrophic cardiomyopathy had a cerebrovascular accident more than 3 years into treatment with idebenone. A magnetic resonance imaging (MRI) scan indicated an ischemic cerebrovascular accident with no hemorrhage and possible thrombophlebitis. The SAE is most likely to be explained by the subject's cardiomyopathy.

Laboratory findings

Haematology results

No clear trend of change in Haemoglobin, hematocrit or WBC were seen in the RHODOS study or overall in the three FRDA studies. However, it was noted that one subject in the NICOSIA study had a low WBC at the month 6 visit (last day of investigational drug).
The applicant has presented a comprehensive and detailed analysis of the WBC including neutrophils and lymphocytes from all individual studies, and, in addition, when combining the data from all studies. No trends for any change in leucocyte, lymphocyte or neutrophil numbers between Baseline and End of Treatment were observed in any clinical studies with idebenone or in pooled data from all studies.

Biochemistry results

There was no evidence observed for an effect of idebenone on any clinical chemistry parameter in the RHODOS study, where results for idebenone were generally similar to those seen with placebo. Likewise, there were no clinically relevant effects on clinical chemistry parameters in FRDA subjects.

However, a 36-year-old Caucasian male, experienced raised liver function tests on routine Study Day 35 of treatment with idebenone 900 mg/day.

Table 24. Liver function tests of a 36-year-old Caucasian male

	AST (U/L)	ALT (U/L)	Gamma GT	Triglycerides
Normal range	1-39 U/L	1-39 U/L	10-49 U/L	0.57-1.70 mmol/L
Screening 26Feb2009	73	37	657	2.60
Baseline 19Mar2009	71	43	747	4.12
Study Day 35 23Apr2009	230	109	1473	4.68

The subject was withdrawn from RHODOS study due to increased liver enzyme values (without bilirubin increase). The event was reported as ongoing. The investigator considered this event severe in intensity and possibly related to study drug. In the FRDA studies there were no consistent indication of an effect on liver enzyme from idebenone exposure. No clear trend of change in liver function (ALT, AST, GGT and bilirubin) has been seen in the analyses of data from clinical trials conducted by the applicant at the CHMP request.

In addition, one Subject in the MICONOS study had notably abnormal creatinine clearance at Week 52 (see also description in section SAEs above). This subject had experienced two SAEs of abnormal creatinine blood levels and acute tubular necrosis, with the abnormal creatinine blood levels resolving and the acute tubular necrosis continuing until the subject was lost to follow up.
At the CHMP request the applicant has presented a comprehensive and detailed analysis of the renal and urinary parameters from all patients included in individual studies and combined the data from all studies. It could be concluded from the analysis that treatment with idebenone at doses of up to 2250 mg/day has no effect on renal function. In light of this, the renal tubular necrosis reported in the MICONOS study is considered as coincidental and unrelated to the study drug.

Urinalysis

Chromaturia was reported in one subject in the NICOSIA study and several subjects in the IONIA study. This is explained by metabolites of idebenone that are coloured and may cause chromaturia, i.e. a reddish brown discoloration of the urine. This effect is harmless, not associated with haematuria, and does not require any adaptation of dose or discontinuation of treatment.

ECG

Only small changes in the ECG parameters were observed (heart rate, PR interval, QRS interval, QT interval and QTc interval corrected using Bazett's formula: QTcB) from Screening to Week 24 or to follow up in both treatment groups in the RHODOS study. There was no evidence of a prolonged QTcB interval after treatment.

Table 25. Summary of ECG results in RHODOS study

Parameter (units)	Idebenone (N=55)			Placebo (N=30)		
	Screening Mean (SD) (n=54)	Week 24 Mean (SD) Change (n=41)	Follow-up Mean (SD) Change (n=9)	Screening Mean (SD) (n=30)	Week 24 Mean (SD) Change (n=21)	Follow-up Mean (SD) Change (n=8)
Heart rate (bpm)	67.15 (13.039)	-0.71 (9.978)	2.11 (10.069)	65.80 (13.423)	0.48 (10.856)	4.63 (7.726)
PR interval (ms)	160.6 (27.789)	1.34 (26.943)	6.44 (18.541)	160.0 (31.217)	-2.10 (13.616)	-2.50 (34.105)
QRS interval (ms)	92.98 (16.245)	2.10 (12.387)	4.44 (7.683)	94.67 (12.620)	0.19 (9.031)	-2.63 (11.747)
QT interval (ms)	374.9 (37.903)	-8.76 (83.723)	8.33 (28.062)	381.5 (32.170)	-17.0 (64.893)	-17.1 (25.632)
QTcB interval (ms)[1]	392.0 (27.975)	-9.78 (83.409)	15.00 (28.253)	395.8 (32.830)	-14.6 (70.845)	-3.88 (16.941)

Source: RHODOS CSR Table 14.3-5.1

[1] QTcB interval calculated as: QT/square root of (60/heart rate)

There were no significant changes in ECG measurements in any of the FRDA double-blind studies.

In conclusion, no clear signal of ECG changes or cardiac effects of idebenone have been documented.

No safety concerns related to QT prolongation are raised in the extensive pre-clinical program or in the analysis ECG data from the clinical program. Therefore, no thorough QT-study is judged to be necessary.

Vital signs

There were no significant changes in vital signs reported.

Safety in special populations

The applicant has not conducted any studies on renal and hepatic impairment. This is considered acceptable, given the overall safety profile of idebenone and the rare disease being treated.

There is likely no pharmacokinetic interaction with oral contraceptives based on the absence of induction potential by idebenone/QS10.

Idebenone has not been studied in pregnant women. To date five cases of idebenone exposure during pregnancy have been reported. Spontaneous abortion seems to be higher than expected (three out of five cases of pregnancy reported have resulted in spontaneous abortion). At the CHMP's request the applicant has analysed this finding in more detail and based on the observations in the literature and data in FRDA patients, the incidence of cases of spontaneous abortion noted seem to fall within the statistical variability of the data-set analyzed.

No data are available in paediatric patients under the age of 14.

Safety related to drug-drug interactions and other interactions

No in vivo drug interaction studies have been performed in this clinical program.

Discontinuation due to adverse events

One patient in the RHODOS study was withdrawn from the study due to increased liver enzyme values (without bilirubin increase) and associated AEs (see Laboratory findings section).

In two patients on active treatment in the MICONOS study diarrhoea, and in addition in one of these patients, vomiting caused withdrawal from the study drug.

Post marketing experience

As of 31-Mar-2011, Santhera has knowledge of 116 AE spontaneous reports for idebenone in the FRDA indication.

Thirty-six of these AEs (12 serious and 24 non-serious) were received with Mnesis 45 mg, via Takeda from France and Switzerland. The most frequent AEs from these two countries were fatigue and gait disturbance, most likely related to the underlying disease. Of the serious reports, one described fulminant hepatitis and multi-organ failure in a 40-year old male subject with FRDA, and the other was a 14-year old male with FRDA-related hypertrophic cardiomyopathy who had a cerebrovascular accident more than 3 years into treatment with idebenone (see Serious adverse event section).

In Canada, Santhera markets Catena, a high-strength formulation of idebenone (150 mg oral tablet), under a Notice of Compliance with Conditions (NOC/c) for the indication “symptomatic management of patients with Friedreich’s Ataxia”. 80 AEs were reported from Canada, of which 20 were serious (15 with the 450/900 mg/day dose and 4 with the 1350/2250 mg/day dose; in one case the dosage was not provided) and 60 were non-serious (51 with the 450/900 mg/day dose and 7 with the 1350/2250 mg/day dose; for 2 AEs the dosage was not provided).

The AEs most frequently reported were minor gastrointestinal events such as nausea, vomiting, diarrhea and abdominal pain. Seven reports of lack of efficacy with no associated AEs were also received.

One fatal case was reported spontaneously from Canada (case ID SAN000158). It concerned a 21-year old male with FRDA and a history of epilepsy who had a seizure while swimming in a lake and drowned.

Seventeen SAEs were reported: Inflammation (feet swelling), medically important hyperkalemia, rash, pruritus and face swelling, atrial fibrillation leading to hospitalization, a manic episode led to the hospitalization, congestive cardiac failure, fall, dyspnea and vomiting leading to hospitalization, elevated liver enzymes.

2.6.1. Discussion on clinical safety

Mild or moderate diarrhoea is the most common AEs related to idebenone exposure. This adverse event can be handled by the patient and are normally without serious risks for the patient.

Chromaturia was reported in one subject in the NICOSIA study and several subjects in the IONIA study. This is explained by metabolites of idebenone that are coloured and may cause chromaturia, i.e. a reddish brown discoloration of the urine. This effect is harmless, not associated with haematuria, and does not require any adaptation of dose or discontinuation of treatment. However caution is recommended in order to ensure that chromaturia does not mask changes of colure due to other reasons.

The applicant has not conducted any studies on renal and hepatic impairment. This is considered acceptable, given the overall safety profile of idebenone and the rarity of the disease being treated.

Abnormal haemoglobin, hematocrit or WBC values were seen in the RHODOS study or overall in the three FRDA studies. Therefore it is advisable that the results for a complete blood cell count (CBC) should be available before initiating treatment with idebenone and that CBC should be repeated one month after initiating the treatment with idebenone, and then at 3 months and at 6 months, and 6-monthly thereafter.

Post marketing rash, pruritus and face swelling were reported by a 17-year-old male consumer treated with idebenone 2250 mg/day. Allergic reactions are also listed in the Canadian Product Monograph. Consequently idebenone treatment should not be given to patients that are hypersensitive to the active substance or to any excipients.

No in vivo drug interaction studies have been performed in this clinical program.

The use of idebenone in pregnant and lactating women, in children under 14 years of age, in elderly patients and in patients with hepatic and renal impairment should be considered as missing information.

The most relevant safety data for LHON patients are derived from RHODOS study. There is no relevant safety information about idebenone beyond the 6 month exposure of the study (only further 5 patients were being receiving idebenone after finishing RHODOS study). In order to address this issue the applicant is requested to collect long-term (up to five years) safety data in LHON patients by means of a Product Exposure Registry.

2.6.2. Conclusions on the clinical safety

Hypersensitivity to the active substance or to any excipients has been identified as the only contraindication.

Diarrhea (very common) was identified as the only most common AE related to Idebenone exposure. This AE is normally easy to handle for the subject on treatment.

In general, the overall incidence of SAEs was low and none of them have been documented that clearly related to Idebenone exposure. Additionally, treatment discontinuations as a result of AEs were considered to have in general a low incidence.

The CHMP considers the following measures necessary to address the missing safety data in the context of a MA under exceptional circumstances: To collect long-term (up to five years) safety data in LHON patients by means of a Product Exposure Registry.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to conclude on pharmacovigilance and risk minimisation activities at this time.

2.8. Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan.

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show 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

Benefits
Beneficial effects

The main body of evidence supporting the efficacy of idebenone in LHON is represented by the results of the pivotal trial included in this application (RHODOS).

In the overall population studied, the primary endpoint – Best Recovery - did not reach statistical significance (p=0.291) and the difference in VA between treatment arms was not clinical relevant (3 letters in favour of idebenone). Potential benefits were demonstrated in analyses of the key secondary endpoint – Best Visual Acuity, the endpoint regarded of higher clinical relevance. For this endpoint, a non-significant (P=0.078) and not clinical relevant effect (logMAR -0.120, 6 letter difference) was shown in the overall LHON population. However, the 95% CI (-0.255, 0.014) indicated that idebenone could lower the risk for a substantial loss of vision

However, a restricted target population has been identified, corresponding to patients presenting for treatment within one year of treatment regardless of the mutation type. Statistically significant and clinically relevant effect of idebenone on visual acuityhas been demonstrated in this sub-group. In this subset (n = 28 patients; n= 19 on idebenone treatment; n= 9 on placebo) a difference from baseline to Week 24 of 17 letters (p = 0.016) in favour of idebenone has been shown for the main secondary efficacy end-point, best visual acuity at week 24 compared to best visual acuity at baseline, considered to be the endpoint of highest clinical relevance,.

These results are consistent with other related outcomes (such as the response by individual eyes count) and presented literature data.

Uncertainty in the knowledge about the beneficial effects

Formally, RHODOS study is a failed single pivotal trial of an exploratory nature and the inconclusive outcome in a full LHON population cannot be ignored.

Although a consistent trend in the effect (considered clinically meaningful) in the selected target population is observed, there is a significant degree of uncertainty of the robustness of data (i.e mainly due to potential confounders and the limited size of the population). In this respect the powerful effect of inclusion or exclusion of patient 23 on the results of the efficacy analysis is an indicator to which extent such confounder (e.g. spontaneous regression) has on the effect measured in the target population.

Concerns over the true nature of the measured effect have been raised. A favourable natural course of disease in patients carrying the selected mutations is not expected. However, improvement was reported in some idebenone patients before being treated although this did not affect the overall effect of the RHODOS study.

The above uncertainties were also expressed by the expert panel. Due to insufficient data, the expert panel was not able to indicate either whether the idebenone effect seen in the overall LHON population is biologically plausible. In addition, the experts considered the effect observed as functionally relevant from a clinical perspective although the number of patients was so small that they were not able to

exclude that the clinical effect could be at least in part the result of spontaneous regression of the disease.

The maintenance of effect has not been conclusively demonstrated. Even though the treatment effect difference between the idebenone and placebo arms has been almost the same 2 years after the treatment was stopped, the trend to positive evolution of patients in both arms was seen. This finding could be at least in part attributed to patients' ability to learn to use extrafoveal vision in patients with central scotoma. Whether other factors, such as the reduction of the sample size (only 58 out of 85 patients were included in the follow-up visit), the use of off-label idebenone in 5/58 subjects or the possible higher retention of those more favourable cases could have impact on the final outcome should also be taken into consideration. Therefore, and although in principle no signals of spontaneous recovery are observed, firm conclusions cannot be drawn.

Risks

Unfavourable effects

Hypersensitivity to the active substance or to any excipients has been identified as the only contraindication.

Diarrhea (very common) was identified as the only most common AE related to Idebenone exposure. This AE is normally easy to handle for the subject on treatment.

In general, the overall incidence of SAEs was low and none of them have been documented that clearly was related to Idebenone exposure. Additionally, treatment discontinuations as a result of AEs were considered to have in general a low incidence.

Uncertainty in the knowledge about the unfavourable effects

The safety analysis is mainly based on a very limited number of subjects with LHON (51 subjects exposed for 24 weeks), but supported by safety data from double blind studies (160 subjects exposed for 12 months) and an open extension study (subjects followed for up to 382 days) including subjects with FRDA whom are exposed to similar or higher doses. Data from the study RHODOS-OFU provides longer exposure of only further 5 patients. The most relevant safety data for LHON patients are derived from RHODOS study. There is no relevant safety information about idebenone beyond the 6 month exposure of the study.

In vitro inhibition and induction studies have been submitted. While no significant systemic inhibition/induction was evident, intestinal inhibition of CYP3A4 cannot be excluded.

There are also no data on the use in patients with renal or hepatic impairment.

Benefit-risk balance

Importance of favourable and unfavourable effects

LHON affects primarily young adults and is associated with poor vision prognosis. Despite the limitations of the RHODOS study, the effect shown is considered as clinically relevant in the subgroup of the LHON population presenting for treatment within one year of onset of symptoms.

The safety profile of idebenone can be considered benign.

Benefit-risk balance

A clinical relevant effect has been observed in a subgroup of LHON patients with onset of the disease within one year (target population). However, given the limited size of such subgroup of patients and the lack of biological plausibility of idebenone effect, the uncertainties related to the true nature of the observed effect remain too large. Therefore, despite the relatively benign safety profile of the drug the benefit-risk balance for idebenone in the proposed indication is considered negative.

Discussion on the benefit-risk balance

The limitation of this dossier are related to the orphan disease and the difficulties to conduct a clinical development that provides robust data in the proposed target population ("Patients with Leber's Hereditary Optic Neuropathy (LHON) presenting for treatment within one year of onset of symptoms").

In spite of the apparent benign safety profile, the lack of robustness of the data presented precludes the conclusion on whether the effect of idebenone has been overestimated. Even recognizing the relevance of the observed effect the number of patients on which the efficacy relies on is so small that it cannot be excluded that the clinical effect could be at least in part the result of spontaneous regression of the disease.

To address the uncertainties regarding the effect, a confirmatory placebo-controlled study would optimally be performed. However, the rarity of patients identified in the target indication questions the feasibility of such study. A Product Exposure Registry, in which patients treated with idebenone could be periodically assessed for efficacy and compared with historical controls has been proposed by the applicant as a specific obligation. However the benefit-risk balance in the proposed indication is considered negative and the product registry may not provide sufficient evidence with respect to clinical efficacy.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy for Raxone in the treatment of patients 14 years of age and older with Leber's Hereditary Optic Neuropathy (LHON) presenting for treatment within one year of onset of symptoms, the CHMP considers by majority decision that the efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and therefore, pursuant to Article 12(1) of Regulation (EC) No 726/2004, recommends the refusal of Marketing Authorisation under exceptional circumstances for the above mentioned medicinal product.

The CHMP considers that:

The single pivotal trial failed to show a clinically and statistically relevant therapeutic effect of idebenone in the recruited population of Leber's hereditary optic neuropathy. The claim of statistically significant efficacy is based on the results observed in a small subgroup of patients with recent onset of the disease and there are insufficient data to fully elucidate the biological plausibility of the effect of idebenone across the spectrum of the Leber's neuropathy population. Furthermore, the reliability of the efficacy results of idebenone in the proposed target population (patients for treatment within one year of onset of symptoms regardless the mitochondrial mutation type) is questioned. Given the

limited size of such subgroup, the influence of data from individual patients and the possibility that the clinical effect seen could be due to a spontaneous regression or adaptive change to the disease cannot be ruled out.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system and risk management plan to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Divergent positions to the majority recommendation are appended to this report.

APPENDIX

DIVERGENT POSITIONS

Divergent Positions

The undersigned members of the CHMP did not agree with the CHMP's opinion recommending the refusal of the granting of a Marketing Authorisation for Raxone.

The reasons for divergent positions were as follows:

Despite the limitations of the Rhodos study, the effect shown in this trial on visual acuity is considered as clinically relevant in the LHON population presenting for treatment within one year of onset of symptoms. There was a difference of 17 letters with respect to placebo and more patients on idebenone experienced an improvement while fewer subjects showed a deterioration of the visual acuity. The favourable effect of idebenone in visual acuity has been indicated in all analyses conducted. In addition, there is further support from published retrospective studies.

The apparent benign safety profile of idebenone seems to overrule the uncertainties related to the lack of robustness of efficacy data in a condition without therapeutic alternatives. Given that a new confirmatory placebo-controlled study could be difficult to be performed within a reasonable time-frame a prospective efficacy analysis within the planned registry with the use of historical controls appears currently a sufficiently valid and feasible option to obtain some additional, even though not exhaustive, short- as well as long-term efficacy data.

London, 17 January 2013

……..……	…….
John Joseph Borg	Kristina Dunder
……..……	……..……
Concepcion Prieto Yerro	Mila Vlaskovska
……..……	……..……
Daniela Melchiorri	Piotr Fiedor
……..……	……..……
Jacqueline Genoux-Hames	Jean-Louis Robert
……..……	……..……
Stanislav Primozic	Pieter Neels
……..……	……..……
Agnes Gyurasics	Emilia Mavrokordatou