Single Technology Appraisal

Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Chiesi:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Initial response
   b. Further response

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Leber's Hereditary Optic Neuropathy Society (LHON Society)
   b. Royal College of Ophthalmologists (RCOphth)
   c. NHS England

4. **Expert personal perspectives** from:
   a. James Ferguson, Trustee of LHON – patient expert nominated by Leber's Hereditary Optic Neuropathy Society
   b. Lily Mumford – patient expert nominated by Leber's Hereditary Optic Neuropathy Society
   c. Professor Marcela Votruba, Professor and Hon. Consultant in Ophthalmology – clinical expert nominated by Royal College of Ophthalmologists
   d. Professor Patrick Yu Wai Man, Professor of Ophthalmology and Honorary Consultant Ophthalmologist – clinical expert nominated by Royal College of Ophthalmologists

5. **External Assessment Report** prepared by BMJ

6. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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Document B

Company evidence submission

November 2023

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Abbreviations

ABN	Association of British Neurologists
AE	Adverse events
AMA	American Medical Association
AMD	Age-related macular degeneration
ARMD	Age-related macular degeneration
ATP	Adenosine triphosphate
BCVA	Best-corrected visual acuity
CAP	Centrally authorised product
CaRS	Case Record Survey
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CF	Count fingers
CGIC	Clinical Global Impression of Change
CRB	Clinically relevant benefit
CRR	Clinically relevant recovery
CRS	Clinically relevant stabilisation
EAG	External Assessment Group
EAP	Expanded Access Program
EC	European Commission
EMA	European Medicines Agency
EMC	Electronic Medicines Compendium
ERG	Evidence Review Group
ETDRS	Early Treatment Diabetic Retinopathy Study
HRQoL	Health related quality of life
HTA	Health technology assessment
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
ITT	Intent-to-treat
KOL	Key opinion leader
LHON	Leber's hereditary optic neuropathy
LOCF	Last observation carried forward
logMAR	Logarithm of the minimum angle of resolution
LP	Light perception
LV	Last observation visit
LY	Life years
MA	Marketing authorisation
MMRM	Mixed-Model for Repeated Measures
MRI	Magnetic resonance imaging
NHB	Net health benefit
NICE	National Institute for Health and Care Excellence
OGC	Ocular Genetics Clinic
OWSA	One-way sensitivity analysis

PAS	Patient access scheme
PASLU	Patient Access Schemes Liaison Unit
PP	Per protocol
PS	Proportional shortfall
PSA	Probability sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Preferred term
QALY	Quality-adjusted life years
QoL	Quality of life
QS	Quality-adjusted life years shortfall
RCP	Royal College of Physicians
RCT	Randomised controlled trial
RGC	Retinal ganglion cells
RNFL	Retinal nerve fibre layer
ROI	Republic of Ireland
RVO	Retinal vein occlusion
RWE	Real-world evidence
SAE	Serious adverse events
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
TTO	Time-trade off
UAMS	University of Arkansas for Medical Sciences
VA	Visual acuity
VAS	Visual Analog Scale
VF	Visual function
WTP	Willingness-to-pay

B.1 Decision problem, description of the technology and clinical care pathway

Leber's hereditary optic neuropathy (LHON) is an ultra-rare and severely disabling maternally inherited neurodegenerative mitochondrial disease, primarily affecting young adult males. LHON targets the optic nerve, leading to rapid loss of vision.(1,2)

The estimated prevalence of LHON mutation is approximately 1 in 50,000 people worldwide.(3) This translates to approximately 975 people with LHON in England, considering the estimated population of individuals aged 12 years and above in 2021.(4,5) Only a proportion of the total population carrying the LHON mutation (estimated as 10% of females and 50% of males) will develop optic neuropathy.(6) As a result, the actual incidence of vision loss is expected to be lower that the prevalence figure, with an estimated number of LHON patients carrying the mutations and affected by vision loss to be approximately 289 patients in England.

LHON is a debilitating condition which significantly impacts patients' quality of life, causing significant disruption to their education, careers, and family life.(7–9) LHON also affects the quality of life of caregivers, impacting their lives, emotional wellbeing and employment.(7)

Diagnosis of LHON is mainly based on patient and family medical history, neuro-ophthalmological examination and mitochondrial deoxyribonucleic acid (mtDNA) genetic testing.(10) Diagnosis of LHON is often delayed due to the rarity of the disease and the diverse clinical presentation.(10)

Current treatment options for patients with LHON in England do not target the underlying neurodegenerative condition and are limited to non-pharmaceutical standard of care which comprises an extensive list of lifestyle management (avoiding alcohol, tobacco, exposure to drugs and toxins with mitochondrial toxicity), genetic counselling and supportive treatments.(11) There is an unmet medical need in the management of LHON as the current standard of care do not prevent vision loss or allow recovery of visual function.(11,12)

Idebenone is the first and only licensed treatment option for visual impairment in adolescents and adults with LHON.(13) Idebenone has demonstrated the potential to reactivate viable-but-inactive retinal ganglion cells (RGCs) in LHON patients.(14) Idebenone has already been granted national reimbursement in Wales and Scotland.(15,16) The clinical efficacy and safety profile of idebenone have been demonstrated in several key clinical trials such as the RHODOS and RHODOS-OFU clinical studies, the Expanded Access Programme and LEROS real-world evidence studies.(12,17–22)

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation of idebenone for the treatment of visual impairment in adolescent and adult patients with LHON. Please refer to Table 1 for a summary of the decision problem.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the Company submission	Rationale if different from the final NICE scope
Population	People aged 12 years and older with Leber's hereditary optic neuropathy (LHON)	As per NICE scope	N/A
Intervention	Idebenone	As per NICE scope	N/A
Comparator(s)	Established clinical management without idebenone including: • Visual aids. • Occupational and low vision rehabilitation. • Lifestyle management (no smoking, reduced alcohol consumption, diet that includes fresh fruit and vegetables).	As per NICE scope	As per NICE scope
Outcomes	The outcome measures to be considered include: • Visual acuity (VA) • Contrast sensitivity • Retinal nerve fibre layer • Visual field assessment • Adverse effects of treatment	The outcome measures included are: • VA • Contrast sensitivity • Retinal nerve fibre layer • Visual field assessment • Adverse effects of treatment	As per NICE scope

	• Health-related quality of life	• Health-related quality of life	
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account. The cost-effectiveness analysis should include consideration of the benefit in the best- and worst-seeing eye.	The Company is broadly aligned with the overview of the economic analysis outlined in the final scope, except for the cost-effectiveness analysis, which includes consideration of the benefits in the best- and worst-seeing eye. The cost-effectiveness analysis will only include consideration of the benefit in the best-seeing eye as logMAR VA is measured in the better-seeing eye rather than the worst-seeing eye.	Brown *et al.* (1999) demonstrated that a patient's quality of life is attributed more by the better-seeing eye than the worst-seeing eye (23). The better-seeing eye has a higher predictability and consistency when measuring quality of life compared to the worst-seeing eye (23). Furthermore, change in best VA was the main secondary endpoint in the RHODOS trial. It was considered to be the endpoint most relevant to clinical practice and the one that best reflects the impact of the disease on a patient, being the closest related to visual function in daily life (12,17). Furthermore, during protocol assistance the CHMP agreed with the rational for including this endpoint and that it may be more clinically relevant than the primary endpoint analysis (best recovery of logMAR VA between baseline and Week 24).Brown *et al.* (1999) demonstrated that a patient's quality of life is attributed more by the better-seeing eye than the worst-seeing eye (23). The better-seeing eye has a higher predictability and consistency

			when measuring quality of life compared to the worst-seeing eye (23). Furthermore, change in best VA was the main secondary endpoint in the RHODOS trial. It was considered to be the endpoint most relevant to clinical practice and the one that best reflects the impact of the disease on a patient, being the closest related to visual function in daily life (12,17). Furthermore, during protocol assistance the CHMP agreed with the rational for including this endpoint and that it may be more clinically relevant than the primary endpoint analysis (best recovery of logMAR VA between baseline and Week 24). This also aligns with the health technology assessments of idebenone in Wales and Scotland, both of which focused on change in best VA and were granted national reimbursement for patients with LHON (15,16).
Subgroups to be considered	If the evidence allows the subgroups of people with recent vision loss will be considered.	Within B.2, clinical data is presented split by logarithmic minimum angle of resolution (LogMAR) score, disease mutation or by acute and chronic patients.	As per NICE scope.

Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	There are no special considerations relating to issues of equity or equality.	N/A

Abbreviations: LHON – Leber's hereditary optic neuropathy; N/A – Not applicable; NICE – National Institute for Health and Care Excellence

B.1.2 Description of the technology being appraised

Table 2 presents a description of idebenone as a treatment for visual impairment in adults and adolescents aged 12 years and older with LHON. The Summary of Product Characteristics (SmPC) can be found in Appendix C.

Table 2. Technology being evaluated

UK approved name and brand name	Idebenone (Raxone®)
Mechanism of action	Idebenone, a short-chain benzoquinone, is an antioxidant capable of transferring electrons directly to the mitochondrial electron transport chain.(24) According to this biochemical mode of action, idebenone is thought to reactivate viable-but-inactive RGCs in LHON patients by restoring cellular energy (ATP) generation (24). Depending on the time since symptom onset and the proportion of RGCs already affected, idebenone can promote recovery of vision in patients who experience vision loss (24).
Marketing authorisation/CE mark status	Idebenone was first granted a marketing authorisation by the European Medicines Agency (EMA) on the 08th September 2015.(12) As a result of Brexit, the EU licence for idebenone, which has an existing centrally authorised product (CAP) marketing authorisation (MA), was subjected to grandfathering process and was issued with a Great Britain Product Licence (PLGB) MA number effective from 1st January 2021.(25) Similarly, the application for Orphan Drug Designation Transfer was submitted on the [redacted], and a positive EMA opinion was received on the [redacted]. The final EC decision is expected by [redacted].
Indications and any restriction(s) as described in the SmPC	In line with the SmPC, idebenone is indicated for the treatment of visual impairment in adolescent and adult patients with LHON (24). The SmPC can be found in Appendix C.
Method of administration and dosage	Idebenone is an oral therapy. Each film-coated tablet contains 150mg idebenone. The licensed therapeutic dose is 900mg/day idebenone (two tablets, three times a day), to be taken with food (24).
Additional tests or investigations	No additional tests or investigations are required. Patients should be regularly monitored according to local clinical practice (24). This was validated by UK clinical experts (26).
List price and average cost of a course of treatment	The list price for a 30-day supply (one pack of 180 tablets) of Raxone® is £6,364.

Patient access scheme (if applicable)	A patient access scheme (PAS) involving a simple discount of [redacted] has been approved by Patient Access Schemes Liaison Unit (PASLU). The net price of idebenone after PAS is [redacted]

Abbreviations: ATP – Adenosine triphosphate; CAP – Centrally authorised products; EMA – European Medicines Agency; LHON – Leber's hereditary optic neuropathy; MA – Marketing authorisation; mtDNA – Mitochondrial deoxyribonucleic acid; PLGB – Great Britain product licence; RGCs – Retinal ganglion cells; SmPC – Summary of Product Characteristics.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

LHON is an ultra-rare and severely disabling maternally inherited neurodegenerative mitochondrial disease that exclusively affects the optic nerve. It is characterised by rapidly progressive loss of vision, particularly in young adults and predominantly affects males.(1,2) LHON is a genetic disease caused by mutations in genes encoding complex I subunits of the mitochondrial respiratory chain. There are three primary mtDNA mutations (m.11778G>A, m.14484T>C, m.3460G>A) which can cause this inherited form of blindness.(27) The dysfunction in complex I leads to energy deficiency and oxidative stress, which then lead to RGC death known as apoptosis, resulting in progressive loss of VA and eventual blindness.(28)

In addition to the above mutations, certain risk factors are also involved in the pathophysiology of LHON. The two most important risk factors for vision loss in LHON are male gender and age – where the average age of onset is 20-30 years.(6,17,29) Other factors such as tobacco use, excessive alcohol intake, head trauma, psychological stress, occupational exposure to chemical toxins and nutritional deficiencies of folate and vitamin B have also been linked as triggers for vision loss in LHON.(2,29–31)

In most cases, LHON typically manifests as painless, subacute, rapid and severe loss of VA and colour vision accompanied by the loss of central vision, leaving only peripheral vision remaining. It commonly affects one eye, with the second eye following a similar progression within a few weeks to months. The condition worsens over time, resulting in blindness typically within one year from the initial onset of disease.(6,12,32)

The rapid and persistent lifelong severe visual impairment that arises in individuals affected by LHON poses a significant humanistic and economic burden for both patients and caregivers. Given its prevalence during the critical years of the second and third decades of life, when individuals are typically advancing in their education and career, LHON frequently leads to reduced working hours, lower wages, unemployment, and even early retirement, all of which contribute to significant productivity losses.(7,33) Carers of LHON patients also experience a profound impact on their social life and relationships.(7,33) In a recent survey conducted by Chiesi (2022), clinicians reported an escalating need for informal caregiver support and an increased duration of caregiving as the severity of vision loss worsens in LHON patients.(34)

Although the exact number of people affected by LHON is still unknown, it is estimated that the prevalence of the LHON mutations is approximately 1 in 50,000 and this prevalence assumption was validated by a UK clinician.(3,26) This equates to an approximate prevalence of 975 people with LHON mutations in England based on the predicted population of England aged 12 years or over in 2021 of 48,743,750.(4,5) It is estimated that only approximately 50% of male and 10% of female carriers of a mutation develop optic neuropathy (damage to the optic nerve) which can result in visual impairment.(6) Therefore, the incidence of visual loss is likely to be much less than the prevalence figure described above. Based on the above assumption and a 50:50 gender split with the mutations, the estimated number of LHON patients in England carrying the mutations and affected by vision loss amounts to 289 patients.

B.1.3.2 Clinical manifestations

B.1.3.2.1 Measurement of visual acuity and definition of blindness

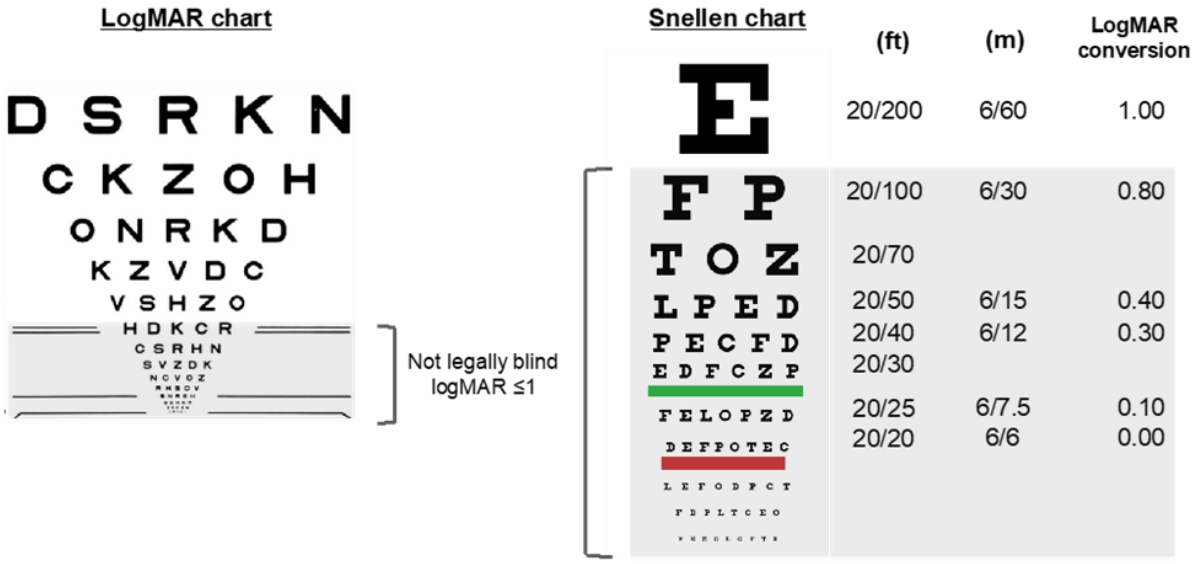
To understand the burden of LHON to patients and carers, it is important to detail how VA is measured, and how this translates to diagnosing vision loss and blindness.

VA, which relates to the sharpness of vision, is usually assessed in clinical trials using the logMAR chart, also known as the ETDRS (Early Treatment Diabetic Retinopathy Study) chart as shown in Figure 1 (left). The chart results are subsequently converted to the logMAR (logarithm of the minimum angle of resolution) scale which quantifies VA based on the number of letters an observer can read on the logMAR or ETDRS chart. The logMAR scale allows measurement from normal vision (score of 0.0), through ‘legally blind’ (score of 1.0), where the observer is only able to read one large letter from six metres distance, all the way to severe visual impairment (score of 1.68), where the observer is only able to read one large letter correctly at one metre distance. (35) In the logMAR chart, each letter has a score value of 0.02 log units. Since there are 5 letters per line, the total score for a line represents a change of 0.1 log units.

Besides the logMAR chart, ophthalmologists may also use the Snellen chart to measure VA, which can be easily converted to logMAR values, as shown in Figure 1 (right). A Snellen chart consists of several rows of letters which gets smaller as the observer reads down the chart. Normal VA is represented as 6/6 on the chart. The two numbers in the result represent distance and the number of lines read whilst the observer is seated. The first number is the distance in metres from the chart when reading it (typically 6 metres but could be 3 metres if the observer is seated closer). (35) For example, on the second line on the chart labelled as 6/30, an observer with standard vision (6/6) could read it from a distance of 30 metres. However, if an observer had a Snellen score of 6/30, they would only be able to read the same line from 6 metres away. In other words, they need to be much closer to the chart to read it. Therefore, a higher second number indicates poorer sight.(35)

The Snellen chart is commonly used in clinical practice for routine vision testing, whereas the logMAR chart is used predominantly in clinical trials and research. Figure 1 shows the relationship between the logMAR chart and Snellen chart, specifically indicating the threshold of not being legally blind.

Figure 1. The logMAR and Snellen chart showing conversion to logMAR (right)



Note on the Snellen chart: The first number given is the distance in metres from the chart when sitting to read it. Usually this is a 6 (for 6 metres) but would be 3 if the person being tested were to sit closer to the chart (3 metres away).
Abbreviation: LogMAR – logarithm of the minimum angle of resolution

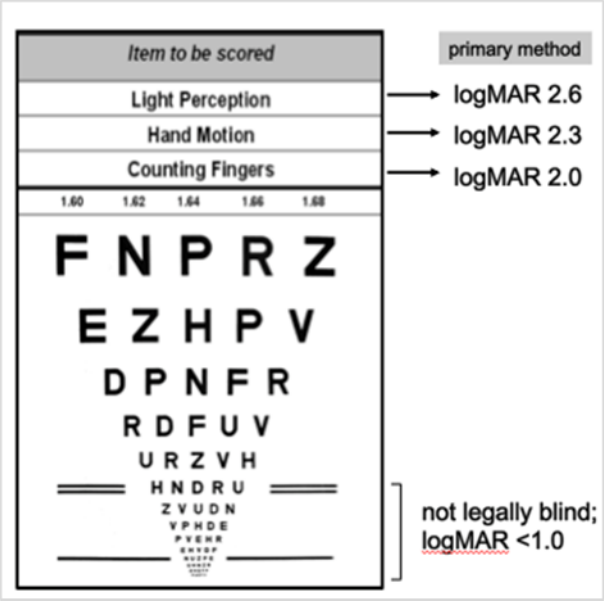
In clinical practice, where the Snellen chart is more commonly used, VA assessment is used in conjunction with visual field measurements (tests to determine how much you can see around the edge of your vision, whilst looking straight ahead) to determine if patients meet the criteria for severe visual impairment or blindness. In the UK, the criteria for being registered as severely sight impaired (blind) are either:

- VA of less than 3/60 as measured on a Snellen chart (logMAR conversion of ≥1.3) with a full visual field, or
- VA between 3/60 and 6/60 as measured on a Snellen chart (logMAR conversion of 1.3 to 1.0) with a severe reduction of field of vision, or
- VA of 6/60 or better (logMAR conversion of ≤ 1.0) as measured on a Snellen chart but with a significantly reduced field of vision, particularly if there is substantial vision loss in the lower part of the field.(35)

Additionally, LHON patients are also classified as having 'off-chart VA' if they are unable to read any letters on the chart. Therefore, to further assess LHON patients with progressively worsened vision, they are scored based on their ability to count fingers (CF) from a distance of 30cm, detecting hand motion (HM) or light perception (LP) (

Figure 2).(8,12)

Figure 2. The logMAR scale showing the 'off-chart VA' categories

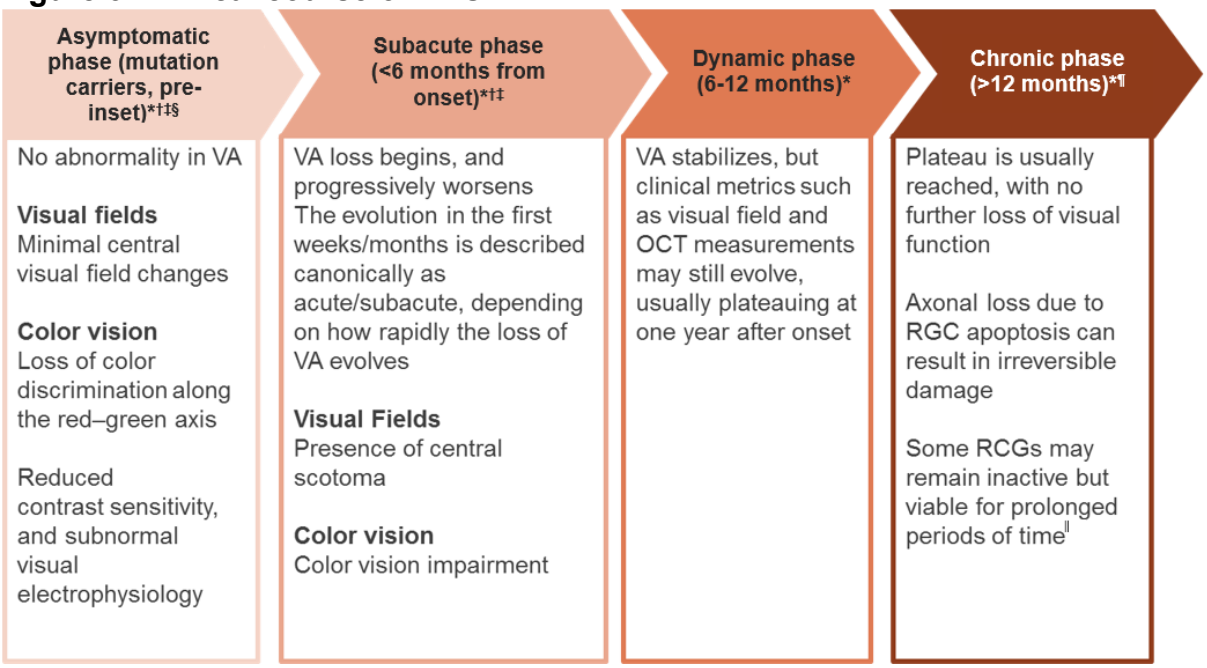


LogMAR values are assessed using the ETDRS charts.(12)
Abbreviation: LogMAR – Logarithm of the minimum angle of resolution

B.1.3.2.2 Clinical course of LHON

According to time from onset, the clinical course of LHON can be categorised into four phases: asymptomatic/pre-symptomatic, acute subacute, acute dynamic and, chronic/atrophic (Figure 3). Over time, the deterioration of VA worsens as they progress through the stages which are described in Figure 3 below.(1,10,30,36)

Figure 3. Clinical course of LHON



Optic disc atrophy associated with chronic phase of the disease usually starts within six weeks of disease onset (30)
*Carelli V et al, 2017(10); †Yu-Wai-Man P et al, 2011(30); ‡Yu-Wai-Man P et al, 2009(1); §Newman NJ et al, 2006(37); ¶Gueven N, 2014(36); ‖Howell N, 1998(38).
Abbreviations: LHON – Leber's hereditary optic neuropathy; OCT – Optical coherence tomography; RGC – Retinal ganglion cell; VA – Visual acuity.

VA in an individual eye reaches its lowest point, also known as 'nadir', in the subacute phase, around four to six weeks after the onset of symptoms and is often reduced to a severity that would be classified as severely sight impaired, or "legally blind". This is confirmed with VA data from a natural history population which revealed that LHON patients experience very rapid loss of VA with over 50% of eyes deteriorating to logMAR above 1.0 within one Week of disease onset, and by 12 months in the dynamic phase, more than 80% of patients were classified as 'legally blind'. VA loss was not commonly recovered, and in 142 observations available for 12-24 months of onset, 78% of all eyes remained legally blind.(39–41)

Whilst in most cases, LHON leads to permanent vision loss, a small minority of patients show spontaneous recovery of VA by a mechanism that is not yet understood. VA recovery, when it occurs, typically happens between six and twelve months after the onset of the initial vision loss. As the acute (subacute and dynamic) phase of LHON is associated with functional loss of RGCs, there is a possibility for natural vision recovery and pharmacological intervention could help rescue VA.(36) In some cases, patients in the chronic phase may still have viable RGCs that could be reactivated through pharmacological treatment, even long after the initial onset, which has been confirmed by recent reports. However, a recovery of meaningful vision is rare and the underlying mechanism behind this spontaneous recovery is poorly understood.(12,42)

B.1.3.2.3 Clinical features

The main clinical feature of LHON is the dysfunction of the optic nerve, resulting in rapid and severe loss of VA, dyschromatopsia (deficiency of colour vision), central scotomas (impairment in central vision), followed by a gradual deterioration of peripheral vision.(29,40,43) Although there is a high variation among patients in terms of age of onset, rate of progression and visual loss, the majority of symptomatic patients eventually experience severe visual impairment or blindness which has a detrimental impact on their overall quality of life.(29,40,44) Figure 4 represents a comparison of the visual field between normal vision and vision affected by LHON.

Figure 4. Comparative image of the visual field between normal vision and LHON vision

Source: Santhera Pharmaceuticals AG. Data on file: PharSolution. Raxone® Pharmacotherapeutic Report, 2017.(40)
Abbreviation: LHON – Leber hereditary optic neuropathy.

B.1.3.2.4 Burden of disease

LHON is a debilitating condition which significantly impacts patients' quality of life, surpassing the impact of other ophthalmic disorders.(45) In a study published in 2009, Kirkman and colleagues measured the quality of life (QoL) of LHON patients by interviewing patients using a Visual function index (VF-14) questionnaire. The VF-14 score indicates the level of visual function and ranges from 0 (worst level of visual function) to 100 (best level of visual function). The study reported that patients with LHON have a visual function (VF) score of 25, whereas patients with other ophthalmic disorders - for example, age-related macular degeneration (AMD) have a VF score of 89 and patients with low vision have a score of 54-62. The authors concluded that LHON has a severe negative impact on QoL and has the worst VF compared to other ophthalmic disorders.(45)

LHON typically manifests in young adults during the prime of their lives, causing significant disruption to their education, careers, and family life. The sudden loss of central vision in LHON patients means that they are also not able to see fine detail, read prints or recognise faces. As such, patients often struggle to cope with the vision loss and report extreme difficulties in their daily living.(8) Patients expressed feeling isolated in a bleak world, where their vision loss made it exceedingly challenging to identify people, objects, and situations.(7) Research conducted in the UK also revealed significant psychological distress that LHON patients often suffer including having suicidal thoughts, depression and anxiety, clearly demonstrating the severe impact of LHON.(9)

Unsurprisingly, sight loss has a profound impact on patients' wellbeing, as reported in a qualitative study, that included patients with LHON and caregivers, which demonstrated the detrimental impact of the disease. LHON affects almost all aspects of patients' and caregivers' lives; activities of daily living, emotional functioning, relationships, studies, work, recreation and finances.(7) Caregivers are deeply involved in LHON patients' lives, often rearranging personal activities around patient's needs, sometimes sacrificing their own pursuits.(7) The caregiving responsibilities can also lead many to reduce their working hours or completely stop working.(7) This often leads to caregivers experiencing stress, anxiety and concern for the patient's future.(33)

Patients with LHON would therefore benefit from a treatment that can stabilise any remaining vision (clinically relevant stabilisation or prevention of blindness) and recover vision loss (clinically relevant recovery).

B.1.3.3 Diagnosis

Diagnosis of LHON is usually based on patient and family medical history, neuro-ophthalmological examination and mtDNA genetic testing.(10) The diagnosis of LHON can be a lengthy process.(10) For example, patients initially seek medical attention in primary care or in an emergency department. They then undergo multiple referrals within secondary care before a diagnosis of LHON is reached. Genetic testing, along with several tests as described in the following sections below, are performed to exclude other conditions such as optic neuritis, multiple sclerosis, brain tumours and diabetic retinopathy. This process often takes a long time. It can take an average of over 7 months from onset of symptoms to receiving a confirmed diagnosis for LHON.(2,10) This was validated by UK clinicians who confirmed that the majority of patients are diagnosed within 6 to 12 months.(26)

Clinical presentation of LHON

LHON should be suspected if patients present with the following characteristics:(29)

- Male gender
- Age between 15 to 30 years old
- Painless vision loss
- Initially one eye is affected, followed by the second eye within weeks to months
- Pseudo-optic disc oedema (swelling of the optic disc) and retinal nerve fibre layer thickening
- Positive family history

As diagnosing LHON is a clinical process, suspicion should arise thorough assessment of individuals displaying the subsequent ophthalmologic, extraocular, neuro-imaging, biochemical, and family history findings:(6,10)

Ophthalmologic

- Unilateral or bilateral, painless subacute visual failure that develops during young adult life
- Disk hyperaemia (swelling of the optic nerve), oedema (swelling) of the peripapillary retinal nerve fibre layer, retinal telangiectasia (tiny blood vessels in the retina become enlarged or dilated), and increased vascular tortuosity on fundus examination preceding or during the acute stage of vision loss(1)
- Optic disc pallor (pale discolouration of the optic disc), cupping of the optic disc (enlargement of the cup-to-disc ratio) and optic disc atrophy (optic disc deterioration) (1,29)
- Electrophysiologic investigations demonstrating optic nerve dysfunction and the absence of retinal disease.

Extraocular

- Neurologic abnormalities (postural tremor, peripheral neuropathy, movement disorders, multiple sclerosis-like illness) (1,6,30)
- Nonspecific myopathy (1,6,30)
- Cardiac arrhythmias (1,6,30)
- Psychiatric disturbances (1,6,30)

Neuroimaging

- Magnetic resonance imaging (MRI) is often normal, but may reveal white matter lesions and/or a high signal within the optic nerves (30)

Biochemical

- The respiratory chain defect observed in LHON is comparatively more subtle in nature compared to other mitochondrial genetic disorders. It is characterised by a reduction in the in vitro respiratory rate, typically ranging from 10% to 50%, depending on the specific variant of mtDNA involved (6)

Family history

- Family history of similarly affected individuals (absence of a family history of LHON does not preclude the diagnosis)

The rarity of the disease in clinical practice makes the diagnosis challenging for health care professionals. LHON may be misinterpreted as other diseases due to its varied non-ophthalmologic clinical manifestations (such as extraocular features described above) and cause a considerable delay in the diagnosis.(10) Therefore, a differential diagnosis, using fundus examination and neuroimaging is crucial in ruling out other conditions.(2,10)

Genetic testing

The diagnosis of LHON is established with the ocular manifestations and is usually confirmed by the identification of one of three common mtDNA pathogenic variants (m.11778G>A, m.14484T>C, m.3460G>A) on molecular genetic testing. Molecular testing approaches may include targeted testing, a multi-gene panel, or a complete mtDNA sequencing.(6)

- **Targeted testing.** Three common mtDNA pathogenic variants account for 90%-95% of LHON. Therefore, targeted analysis for one of these three variants is typically the preferred approach for molecular genetic testing compared to other methods:(6)
    - m.3460G>A in MT-ND1
    - m.11778G>A in MT-ND4, present in 70% of affected individuals of northern European descent and 90% of affected individuals of Asian descent
    - m.14484T>C in MT-ND6, commonly found among French Canadians due to a founder effect

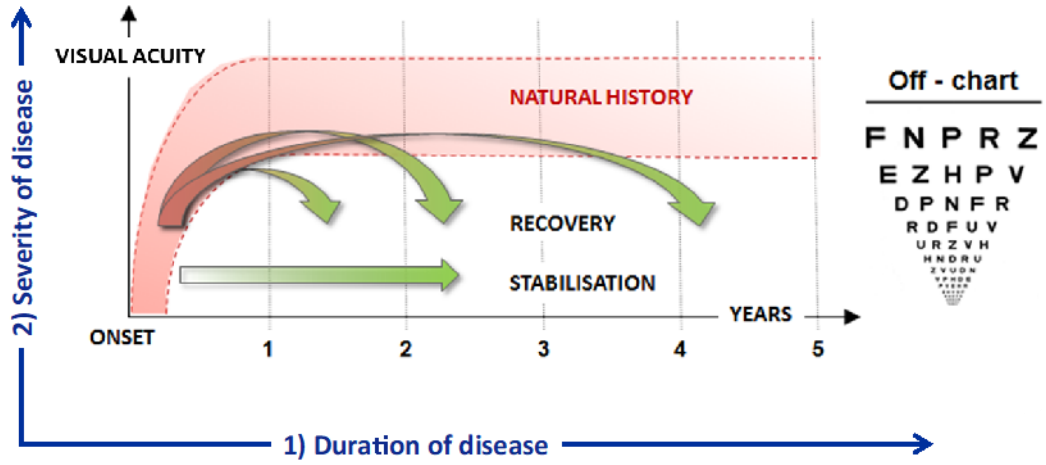
- **A multi-gene panel** that includes the mitochondrial genes that encode subunits of nicotinamide adenine dinucleotide dehydrogenase, including MT-ND1, MT-ND2, MT-ND4, MT-ND4L, MT-ND5, and MT-ND6 can be considered. In very rare cases, nuclear encoded genes that are known to cause LHON may also be included in the panel.(6,46)
- **A complete mtDNA sequencing** may be considered if the use of targeted testing and/or a multi-gene panel did not identify a pathogenic variant and clinical suspicion remains high.(6)

B.1.3.4 Overview of treatment landscape

The treatment goals in LHON are to prevent further vision loss (stabilisation) and to recover lost vision (recovery). To evaluate the effectiveness of these objectives, a clinically relevant benefit (CRB) was defined, which includes both clinically relevant recovery (CRR) and clinically relevant stabilisation (CRS) of VA.

Figure 5 illustrates the natural history progression of LHON from disease onset, where without treatment, VA rapidly deteriorates to 'off-chart' logMAR values (≥1.0) in which LHON patients are eventually classified as legally blind. The green arrows represent the desired therapeutic goals in LHON which are to prevent further vision loss (stabilisation) and to recover lost vision (recovery). As most patients with LHON experience rapid vision loss soon after disease onset, clinical experts therefore consider it crucial to treat LHON patients as early as possible for stabilisation of a good residual VA.(42)

Figure 5. Therapeutic goals in LHON



Green arrows represent desired therapeutic outcomes.
CRS was defined as maintenance of VA <1.0 logMAR in eyes with VA <1.0 logMAR at baseline and a patient is considered to have a CRS if at least one eye had CRS. CRR was defined as an improvement from "off-chart VA" (the equivalent of CF,HM or LP) to at least 1.6logMAR value or an improvement of at least 0.2logMAR value within "on-chart VA". A patient had a CRR if at least one eye had CRR.(19)

B.1.3.4.1 Treatment options

There are currently no specific treatments or guidelines available in England that meet the therapeutic goals outlined above.

In addition to the mtDNA mutations and the main risk factors for LHON; gender, and age, other factors such as excessive tobacco use, heavy alcohol intake, occupational exposure to chemical toxins, nutritional deficiencies have also been linked as triggers to vision loss in LHON.(2,29–31) Considering these risk factors, the current standard of care (SoC) for LHON patients therefore consists of an extensive list involving lifestyle management (avoiding tobacco, alcohol, exposure to drugs and toxins with mitochondrial toxicity),and genetic counselling.(11) Therefore, SoC for LHON primarily focuses on supportive measures based on identified risk factors, such as those described above.

Further to this, patients may also receive supportive treatments for LHON, which include the use of nutritional supplements such as vitamins, coenzyme Q10 and other substances with the aim to improve mitochondrial function, reduce oxidative stress, and provide alternative ATP energy source. Other supportive measures such as low vision aids may also be used to assist patients with severe vision loss. Similarly, near-infrared light therapy, another form of supportive measure, has been shown to improve mitochondrial function and cellular survival in various experimental models. However, these findings are not universally accepted and the mechanisms are poorly understood.(11)

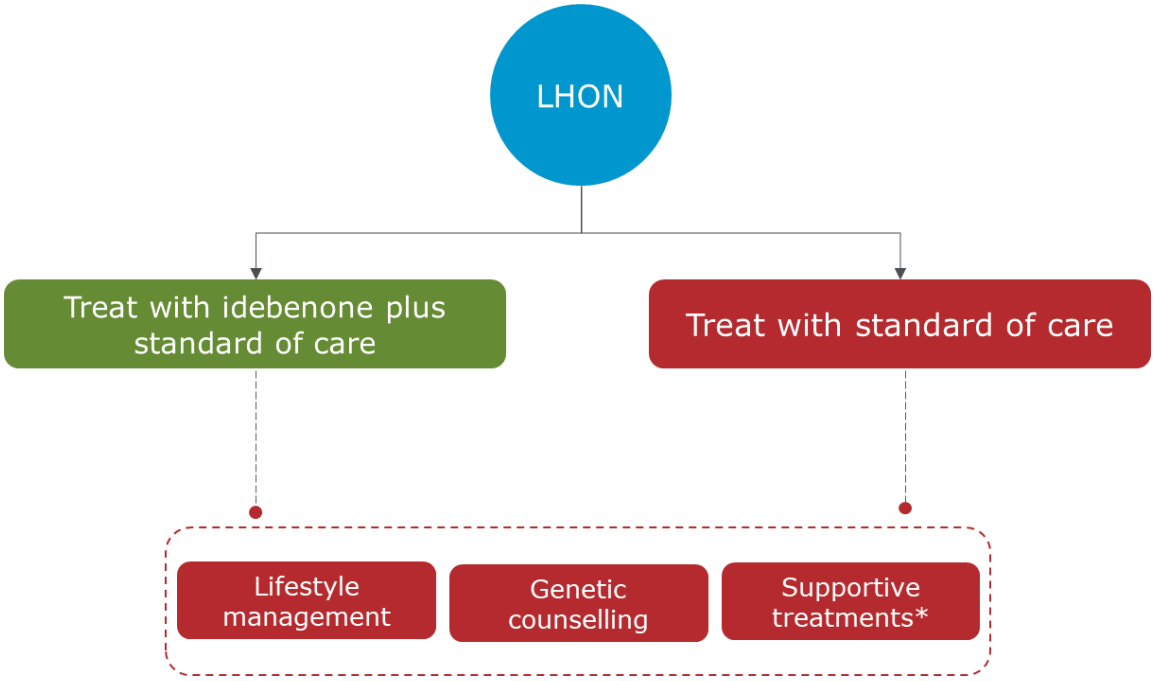
The current SoC for LHON, as described above, does not, however, tackle the underlying genetic condition of LHON, nor does it prevent VF loss or aid in its recovery. Its benefits for patients remain limited, highlighting a significant unmet medical need in the management of LHON.(11)

As a consequence of there being no current established clinical practice for the treatment of LHON in the NHS, idebenone remains the one and only potential treatment for LHON patients.(13)

B.1.3.5 Place of idebenone in treatment pathway

Idebenone would present a step change in the management of LHON as the first and only licensed treatment for patients with LHON in England as current supportive treatments available for LHON patients do not prevent vision loss or allow recovery of VF (11,12), see Figure 6. To be eligible for treatment, patients must have a diagnosis of LHON, based on clinical presentation, medical history and visual loss.(6,10,29)

Figure 6. LHON treatment pathway



*Nutritional supplements such as vitamins, coenzyme Q10. Low vision aids and near-infrared light therapy
Abbreviations: LHON – Leber's hereditary optic neuropathy

Idebenone has demonstrated the potential to reactivate viable-but-inactive RGCs in LHON across the three primary mutations (m.11778G>A, m.14484T>C and m.3460G>A) as well as other rarer LHON-causing mutations.(12) The benefits of idebenone in all LHON segments of patients are demonstrated, regardless of the causative mutations and time from onset.(14) Idebenone's efficacy has been documented up to 5 years after onset in controlled studies and up to 50 years after onset in pilot studies.(12,17–22,42,42,47)

The clinical efficacy of idebenone in preventing vision loss and improving VA as well as the long-term safety data have been demonstrated in key clinical trials such as the RHODOS and RHODOS-OFU clinical studies, the Expanded Access Programme and the LEROS study.(12,17–22,47) These studies present compelling evidence demonstrating the clinical benefits of idebenone and its substantial impact on patients with LHON.(12,17–22,47) When idebenone is introduced early in acute patients, it has the potential to stabilise or recover VA and in chronic patients, it can reactivate viable but dormant RGCs and recover VA.(42)

LHON is a disease associated with high humanistic and economic burden for both patients and informal caregivers. Therefore, the introduction of idebenone has the potential to provide significant life-changing benefits to carers as it could restore a degree of autonomy to LHON patients and reduce the burden on caregivers.(33)

Additionally, idebenone has been granted national reimbursement in Wales and Scotland, clearly demonstrating that idebenone improves health outcomes and patients' QoL and is a cost-effective treatment.(15,16)

Thus, there is a high unmet medical need in the management of LHON in England as the current SoC does not prevent vision loss or allow recovery of VF.(11,12) Idebenone is the only licensed treatment option for patients with LHON that addresses these needs, with the efficacy of treatment supported by the trial data. Therefore, the evidence confirms that idebenone should be made available as soon as possible as a first-line treatment for LHON patients in England.

B.1.4 Equality considerations

There are no known equality issues relating to the use of idebenone in patients with LHON.

B.2 Clinical effectiveness

- The clinical effectiveness of idebenone is demonstrated across several clinical trials and real-world evidence studies, including the RHODOS and RHODOS-OFU trials, an Expanded Access Program (EAP), the LEROS trial, and two Case Record Surveys.
- Treatment with idebenone demonstrated a significant CRB (CRR or CRS of VA) compared with placebo.
    - A composite analysis in the RHODOS intent-to-treat (ITT) population demonstrated a significant CRB with idebenone defined as CRR or CRS of VA compared with placebo (39.6% vs. 10.3% respectively; p=0.0055).(48)
    - In the RHODOS ITT population, three times as many patients treated with idebenone experienced CRR compared with placebo-treated patients (30.2% vs. 10.3% respectively; p=0.056).(48)
    - CRR of vision was observed when treatment with idebenone was started up to ~4 years after onset of symptoms, which indicates that idebenone may reactivate viable-but-inactive RGCs in LHON.
    - Treatment with idebenone demonstrated CRS (maintenance of VA below 1.0 logMAR) of VA in the RHODOS trial (17) and the EAP.(19)
    - Although the primary endpoint ‘best recovery in VA’ did not reach statistical significance due to the short duration of RHODOS trial (24 weeks), the benefit of idebenone was demonstrated by a strong and consistent trend across all endpoints measuring changes in VA.(12,17)
    - In the EAP, CRR from nadir was achieved in 46% of patients and 38.7% of eyes treated with idebenone.(19)
    - Data from the EAP suggest the number of patients experiencing recovery, and the magnitude of recovery, increase with longer treatment duration.(19)
- Idebenone also demonstrated a sustained CRB even after discontinuation of treatment.
    - The results from the RHODOS-OFU study demonstrated that the beneficial effect from 6 months of treatment with idebenone during

RHODOS persisted despite discontinuation of therapy for a median time of 2.5 years.(18)
    - Idebenone recipients who were 'off-chart' at RHODOS baseline and achieved CRR at Week 24 maintained their response at the RHODOS-OFU visit.(18)
    - For change in best VA, the difference between treatment groups from baseline of RHODOS to RHODOS-OFU study visit, was comparable with difference observed at Week 24 of RHODOS (logMAR −0.173 vs. −0.175; 8 letters improvement; p=0.084); thus demonstrating the sustainability of benefit with idebenone.(18)
- Long-term therapy with idebenone was demonstrated to be generally well-tolerated in patients with LHON.
    - In RHODOS, the incidence of all adverse events (AEs) and treatment related AEs were low and similar or lower with idebenone compared to placebo.(12)
    - In RHODOS, AE's reported by ≥10.0% of subjects with idebenone were: nasopharyngitis (25.5%), headache (23.6%), and influenza, increased triglycerides and cough (10.9% each).(12)
    - Data from the EAP suggests that idebenone was well-tolerated with a good safety profile and was in line with the results from the RHODOS trial.(19)

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant literature regarding the efficacy and safety of treatments for LHON. Full details of the methodology and results of the SLR are detailed in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The SLR identified four clinical trials that evaluated the efficacy and safety of idebenone in adult and adolescent patients with LHON: RHODOS, RHODOS-OFU, LEROS and UMIN000017939 trials. The details are provided below:

RHODOS was a double-blind, randomised, placebo-controlled trial assessing the efficacy and safety of idebenone in 85 adolescent and adult patients with LHON. The treatment duration was 24 weeks.(49)

RHODOS-OFU was a single-visit observational follow-up study of 58 adolescent and adult patients with LHON assessing the long-term efficacy of idebenone following participation in the RHODOS trial.(50)

LEROS was an external natural history controlled, open-label intervention study assessing the efficacy and safety of long-term treatment with idebenone in 199 adolescent and adult patients with LHON.(22) The results from LEROS have not been included in the economic model due to heterogeneity between the patient populations. Despite this, results from LEROS have been included in Appendix M to demonstrate the long-term efficacy of idebenone.

UMIN000017939 was a single arm, prospective, interventional, non-comparative study assessing the safety of idebenone treatment Japanese patients with LHON. As this study was conducted in Japan, it is not relevant to the current submission and therefore no results for this study are presented. The treatment duration was similar to the RHODOS study which was 24 weeks.(51)

The real-world evidence (RWE) SLR also identified the Expanded Access Program (EAP), a real-world evidence open-label, multicentre, retrospective analysis of long-term treatment with idebenone in 111 patients with LHON.(52)

Two retrospective, observational natural history studies of patients with LHON, the Case Record Survey (CaRS) (20) and Case Record Survey II (CaRS II), were excluded from the SLR due to their non-interventional nature, which falls outside the SLR criteria. Both surveys provide additional clinical data on the natural progression of LHON and have subsequently been included in the submission. The results of the CaRS study are included in the economic modelling in the SoC arm as they demonstrate the disease course of LHON in patients who only received SoC. Results from the CaRS II study are not yet available so have not been included in the economic modelling. The methodologies of the CaRS and CaRS II studies and the result of the CaRS study are located in Appendix M.

The clinical data in the submission are therefore based on RHODOS, RHODOS-OFU and the EAP. Table 3 to Table 5 detail the clinical evidence from RHODOS, RHODOS-OFU and EAP that is relevant to this submission. Additional supporting clinical efficacy evidence from the LEROS trial and CaRS and CaRS II natural history studies are presented in Appendix M: LEROS trial and Case Record Surveys.

Table 3. RHODOS clinical effectiveness evidence

Study	RHODOS (SNT-II-003) ClinicalTrials.gov registration: NCT00747487(49) Klopstock *et al.* (2011) (17)
Study design	Randomised, double-blind, placebo- controlled, parallel group, multicentre phase II trial performed in three centres: in Munich (Germany), Newcastle (UK), and Montreal (Canada) with 24 weeks treatment duration.
Population	Patients aged ≥14 to <65 years, with impaired VA in at least one eye due to LHON and the onset of visual loss is ≤ 5 years. Patients must also have a confirmed diagnosis by either G11778A, T14484C or G3460A LHON mtDNA mutations at >60% in blood.
Intervention(s)	Idebenone, administered orally at a dose of 300mg (2 x 150mg) three times a day (total daily dose 900mg)
Comparator(s)	Placebo
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	VA • Best CRR of VA in either eye • **Change in best VA** • VA as a continuous variable in both eyes • Proportion of patients in which VA in the initially least affected eye does not deteriorate to 1.0 logMAR or more • VA in best eye at Week 24 compared to VA in best eye at baseline • Number of eyes for which VA improves between baseline and Week 24 Contract sensitivity Retinal nerve fibre layer Visual field assessment **Adverse effects of treatment** HRQoL assessed by VF-14 questionnaire
All other reported outcomes	N/A

Abbreviations: LHON – Leber's hereditary optic neuropathy; logMAR – logarithm of the minimum angle of resolution; mtDNA – Mitochondrial deoxyribonucleic acid; N/A – not applicable; UK – United Kingdom; VA – Visual acuity; VF-14 – Visual function index

Table 4. RHODOS-OFU clinical effectiveness evidence

Study	RHODOS-OFU (SNT-II-003-OFU) ClinicalTrials.gov registration: NCT01421381(50) Klopstock *et al.* (2013)(18)
Study design	Single-visit, observational follow-up study of patients who previously participated in the RHODOS trial, but did not receive any treatment thereafter
Population	Patients who participated in the RHODOS trial.
Intervention(s)	No treatment (previously randomised to idebenone in RHODOS)
Comparator(s)	No treatment (previously randomised to placebo in RHODOS)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	No
Rationale if study not used in model	Long-term efficacy of idebenone is informed in the model by data from the EAP. Patients in the EAP had similar baseline characteristics to those of idebenone-treated patients in RHODOS, and the analysis of logMAR VA was identical between RHODOS and the EAP. The EAP was preferred to RHODOS-OFU for informing long-term efficacy in the model because it collected data at three-monthly intervals, as in the RHODOS trial, whereas RHODOS-OFU was a single-visit follow-up study (median time 2.5 years) of patients who received idebenone or placebo over a 24-Week treatment period during the RHODOS trial.
Reported outcomes specified in the decision problem	VA • **Change in best VA** • Change in VA of both eyes • Change in VA of best eye HRQoL assessed by VF-14 questionnaire

Abbreviations: EAP – Expanded Access Program; HRQoL – Health-related quality of life; logMAR – logarithm of the minimum angle of resolution; OFU – Observational follow-up study; VA – visual acuity; VF-14 – Visual function index

Table 5. Raxone EAP clinical effectiveness evidence

Study	Raxone Expanded Access Programme, EAP (SNT-EAP-001)(52) Catarino *et al.* (2020)(19)
Study design	Open-label, multicentre, retrospective, non-controlled analysis of long-term VA and safety in LHON patients. Idebenone was supplied on a named patient basis to eligible patients not participating in a clinical study.
Population	Confirmed diagnosis of LHON and onset of vision loss in the second eye less than 12 months prior to the date of the Baseline visit (patients that had onset of vision loss for more than 12 months were enrolled but not included in the efficacy population).
Intervention(s)	Idebenone, administered orally at a dose of 300mg (2 x 150mg) three times a day (total daily dose 900mg)
Comparator(s)	No comparator
Indicate if study supports application for MA	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	**VA** • **CRR of VA from nadir**: defined as improvement from "off-chart" to at least five letters or "on-chart" improvement of at least 10 letters. • CRS of VA: defined as maintenance of VA <1.0 logMAR in those with a VA <1.0 logMAR at baseline.
All other reported outcomes	N/A

Abbreviations: CRR – Clinically relevant recovery; CRS – Clinically relevant stabilisation; EAP – Expanded Access Program; LHON – Leber's hereditary optic neuropathy; logMAR – Logarithm of the minimum angle of resolution; MA – market authorisation; VA – Visual acuity

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 RHODOS trial methodology

The RHODOS trial was a randomised, double-blind, placebo-controlled, parallel group, multicentre trial performed in three centres: in Newcastle (UK), Munich (Germany) and Montreal (Canada).(12) RHODOS was the first study in LHON that included patients with the full spectrum of LHON at baseline from early progressive to chronic stages where both eyes were "off-chart".(12)

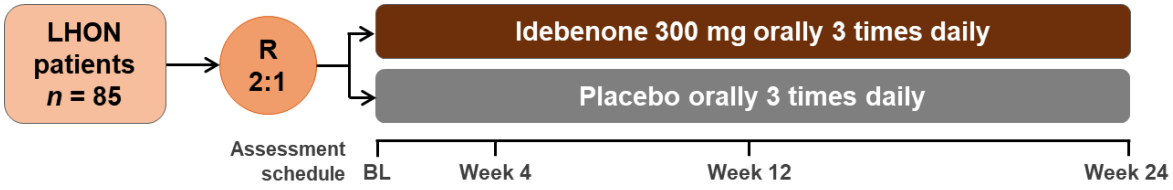
The primary objective of the trial was to determine whether administration of idebenone can improve VF in patients with LHON.(12)

The secondary objectives of the trial were to:

- Determine whether administration of idebenone can mitigate further visual loss in LHON patients entering the trial with an eye less affected than 0.5 logMAR (12)
- Assess changes in Clinical Global Impression of Change (CGIC) and in health related quality of life (HRQoL) (12)
- Assess safety and tolerability following 24 weeks treatment with idebenone (12)
- Explore any relationship between retinal nerve fibre layer (RNFL) thickness and LHON and its treatment with placebo and idebenone in both eyes (12)
- Explore any relationship between colour contrast sensitivity and LHON and its treatment with placebo and idebenone in both eyes (in a subset of patients) (12)
- Explore the relationship between plasma levels of idebenone and measures of efficacy and safety (12)

Patients were randomised to treatment with either idebenone 900 mg/day or placebo in a 2:1 ratio, for a period of 24 weeks. A total of 85 patients were randomised, 55 patients to idebenone and 30 patients to placebo. Patients attended the clinic for six outpatient visits including: a screening visit performed within four weeks of randomisation, the randomisation/baseline visit (Visit 2), Visit 3 after 4 weeks of treatment, Visit 4 after 12 weeks of treatment, Visit 5 after 24 weeks of treatment, and Visit 6 (28 to 35 days after drug discontinuation). Randomisation was stratified by disease history (onset more or onset less than one year prior to randomisation) and by mutation type (G11778A, G3460A and T14484C). The patient and any persons involved in the study (investigators and their site staff, monitors, sponsor and care provider) were blinded to the treatment. Unblinding was allowed when a medical emergency necessitated identification of the study substance the patient had received. After unblinding, the patient did not receive any further study medication and was withdrawn from the study.(12) The design of the RHODOS trial is summarised in Figure 7.

Figure 7. RHODOS trial design



B.2.3.1.1 Eligibility criteria

The RHODOS trial inclusion and exclusion criteria are shown in Table 6.

Table 6. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Patients were included in the study if all of the following inclusion criteria were met at screening (Visit 1) and were confirmed at baseline (Visit 2): • Age ≥14 years and <65 years. • Impaired VA in at least one eye due to LHON. • Onset of visual loss due to LHON was 5 years or less prior to baseline. • Confirmation of either G11778A, T14484C or G3460A LHON mtDNA mutations at >60% in blood. • No explanation for the visual failure besides LHON. • Body weight ≥45 kg. • Negative urine pregnancy test at screening and at baseline (women of child-bearing potential).	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): • Treatment with Coenzyme Q10 or idebenone within 1 month prior to baseline • Pregnancy and/or breast-feeding • Weekly alcohol intake 35 units (men) or 24 units (women) • Current drug abuse • Clinically significant abnormalities of clinical haematology or biochemistry including, but not limited to, elevations greater than two times the upper limit of normal AST, ALT or creatinine • Participation in another clinical trial of any investigational drug within 3 months prior to baseline • Other factor that, in the investigator's opinion, excluded the patient from entering the study • Patients meeting any of the following criteria at any time during the study were to be withdrawn from the study: • Use of any investigational drug other than the study medication during the study period • Pregnancy • Any other significant medical condition

Source: European Medicines Agency. Raxone® (idebenone) European Public Assessment Report 2015 (12)
Abbreviations: ALT – Alanine aminotransferase; AST – Aspartate aminotransferase; LHON – Leber's hereditary optic neuropathy; mtDNA – Mitochondrial deoxyribonucleic acid

B.2.3.1.2 Interventions

Idebenone (2 x 150 mg tablets) or placebo were administered orally three times daily (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. (12)

B.2.3.1.3 Outcomes

The primary efficacy endpoint was the ‘best recovery of logMAR VA between baseline and Week 24 in either right or left eye’ (

Figure **8**, Number 1). In patients with neither eye improving in VA between baseline and Week 24, the change in VA representing the 'least worsening' was evaluated as 'best recovery'.(12,17)

The primary efficacy analysis was performed on the ITT population and repeated as a secondary analysis on the per protocol (PP) population. The difference between groups in the primary efficacy variable was analysed using a repeated measures analysis of covariance (ANCOVA) model with baseline values used as covariate and treatment group, mutation type and disease history as fixed factors. In addition, the visit and interaction between the treatment assignment and visit were included in this model as fixed factors.(12)

A number of sensitivity analyses were performed on the VA outcomes for patients who did not have a quantifiable acuity score, i.e., were off the logMAR scale. Several additional efficacy analyses were performed post-hoc including subgroup analyses based on age (<30 years and >30 years) and absence or presence of discordant VA at baseline (defined as patients with at least two lines difference in VA [logMAR 0.2] between the left and right eye).(12)

The following key secondary efficacy endpoints were measured:

- Change in best VA: Best VA at Week 24 (best eye at Week 24) compared to best VA at baseline (best eye at baseline) was the main secondary endpoint (

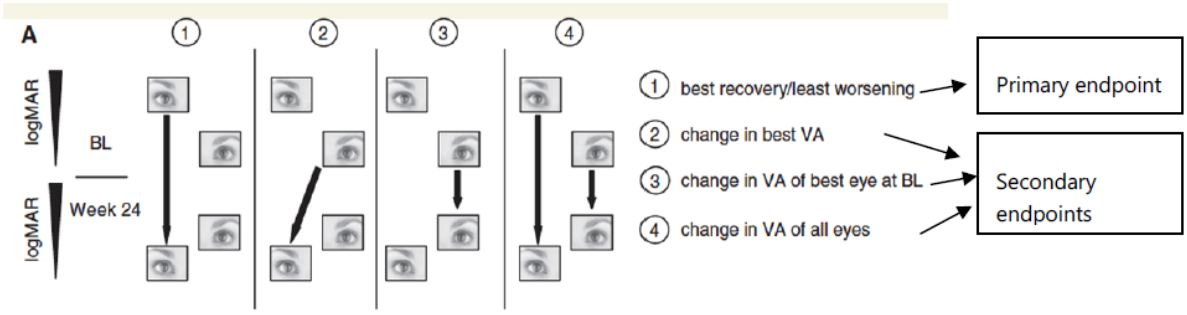
- Figure **8**, Number 2). This is considered to be the endpoint most relevant to clinical practice and the one that best reflects the impact of the disease on a patient, being the closest related to VF in daily life. (12,17) During protocol assistance the CHMP agreed with the rational for including this endpoint and that it may be more clinically relevant than the primary endpoint analysis.

- Change in VA between baseline and Week 24 of the patient's best eye at baseline (

- Figure **8**, Number 3).(12,17)
- LogMAR VA as a continuous variable in both eyes (Change in VA for all eyes) (

- Figure **8**, Number 4). (12,17)

Figure 8. Visual acuity efficacy endpoints (filled arrows) between baseline and Week 24



Source: Klopstock et al, 2011.(17)
Abbreviations: BL – Baseline; logMAR – Logarithm of the minimum angle of resolution; VA – Visual acuity

Additionally, the following other secondary efficacy endpoints were measured:

- Count of eyes/patients for which the VA improves (at least 0.2 logMAR) between baseline and Week 24
- In LHON patients with an eye ≤0.5 logMAR at baseline, the proportion of patients in which the VA in the initially least affected eye does not deteriorate to 1.0 logMAR or more i.e., CRS of residual VA below 1.0 logMAR
- Change in scotoma area as assessed by Humphrey™ 24:2 visual field analysis in both eyes, as a continuous variable
- Change in RNFL thickness as a continuous variable in both eyes
- Change in colour contrast sensitivity as a continuous variable in both eyes (in a subset of patients)
- CGIC change from baseline at Week 12 and Week 24
- Change in HRQoL assessed by VF-14 questionnaire
- Change in self-reported general energy levels assessed by Visual Analog Scale (VAS) from baseline to Week 24
- Plasma levels of idebenone matched to measures of efficacy and safety

To assess the clinical meaningfulness of improvements elicited by idebenone, specific post-hoc responder analyses in RHODOS were conducted. Of particular relevance, are responder analyses using a stringent definition of CRR in patients with the full spectrum of VA loss, which was considered by the CHMP to be a valuable marker for assessing treatment benefit.(12)

- Proportion of patients with CRR from baseline (improvement of at least logMAR 0.2, equal to two lines on-chart) for patients with “on-chart” VA at baseline, or an improvement from “off-chart” VA to at least logMAR 1.6 (equal to one line on-chart) for patients with off-chart VA at baseline)(12)

Further responder analyses included post-hoc were:

- Proportion of eyes with a CRR from baseline.
- Proportion of patients with a clinically relevant worsening (i.e. a change from logMAR ≤1.6 to “off-chart” or a worsening of at least logMAR 0.2, equal to two lines “on-chart”). (12)
- Effect size of changes in patients with CRR.
- Proportion of patients with improvement in primary endpoint and main secondary endpoint.
- Proportion of patients in whom the recovery observed improved the patient's best VA.
- Proportion of eyes with CRR from the VA nadir (the worst VA at any time post-baseline).
- Proportion of patients presenting with CRR from the VA nadir.
- The time to clinically relevant VA recovery.
- Responder analysis for patients who were “off-chart” at baseline.

In addition to these analyses, the overall benefit of idebenone compared to placebo with regards to disease progression was assessed by a composite endpoint which considered two key outcomes which define treatment success: the number of non-legally blind patients stabilising without deterioration to blindness, and the number of patients with a CRR.

When the RHODOS study was initiated, the lack of detailed natural history studies made it difficult to select clinically meaningful trial endpoints to inform *a priori* power calculations. In addition, the optimal timepoints for assessment of a treatment response were not known. Consequently, the RHODOS study was of relatively short duration (24 weeks), which may not have been long enough to fully assess the benefit of idebenone.

B.2.3.1.4 Concomitant treatments

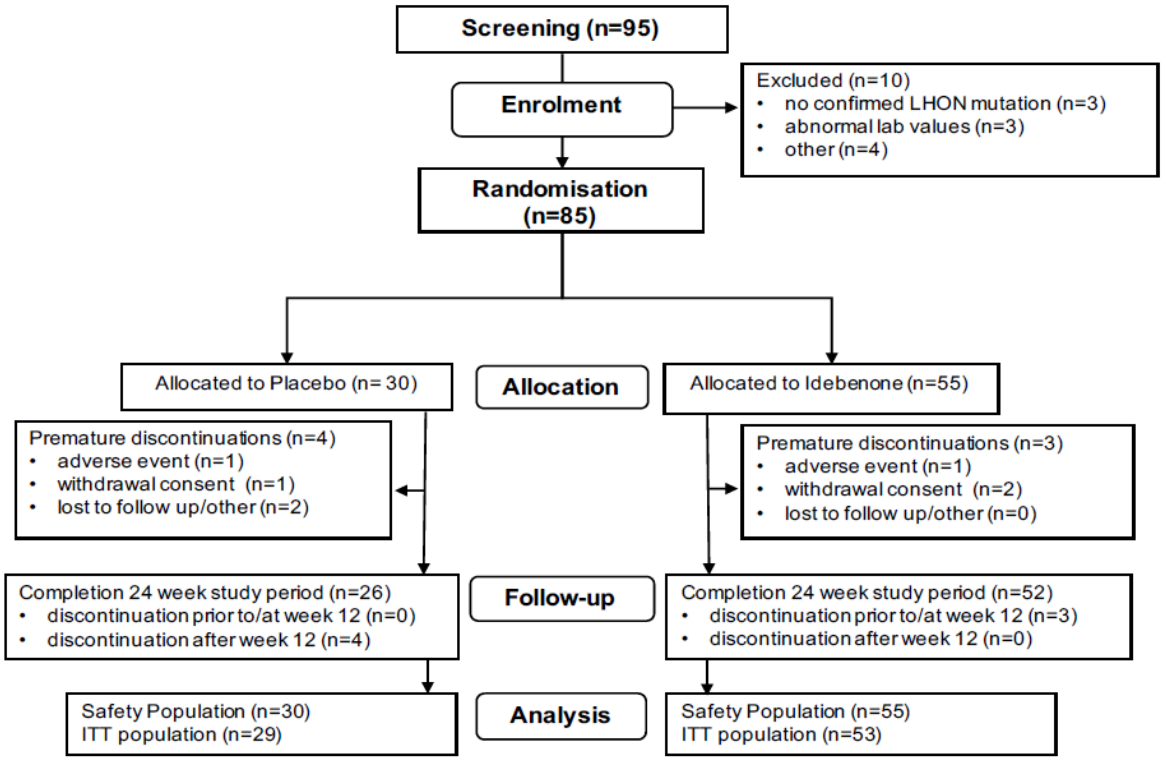
In both treatment groups, the most commonly used concomitant medications were anilides, mostly paracetamol, which were used by 17 patients (30.9%) in the idebenone group (N=55) and 10 patients (33.3%) in the placebo group (N=30) and propionic acid derivatives, mostly ibuprofen, which were used by seven patients (12.7%) in the idebenone group and three patients (10.0%) in the placebo group (12).

B.2.3.2 RHODOS trial population

B.2.3.2.1 Patient disposition

The details of the RHODOS trial patient disposition are depicted in Figure 9.

Figure 9. RHODOS trial patient disposition



Source: European Medicines Agency. Raxone® (idebenone) European Public Assessment Report. 2015(12)
Abbreviations: ITT – Intent-to-treat; LHON – Leber's hereditary optic neuropathy

B.2.3.2.2 Baseline characteristics

The baseline characteristics of the RHODOS study population are summarised in Table 7. Overall, the age, gender and mutation distribution were balanced between the treatment groups.(12,17) Patients enrolled into RHODOS were on average 33 years old, and the vast majority (85.9%) of the participants were male. These individuals had experienced vision loss for on average two years (mean months since onset 23.1 months). This demographic distribution closely mirrors that of LHON patients in real-world setting such as the CaRS. (20) The baseline characteristics of the study have been validated by UK clinical experts as generalisable to clinical practice in England. The trial's population also represents a well-established disease process with rather severe symptoms.(8,29)

Table 7. Baseline characteristics of RHODOS

Characteristic	**Idebenone** (N=55) (N=53 for VA)	**Placebo** (N=30) (N=29 for VA)	**Total** (N=85) (N=82 for VA)
Age, mean ± SD [median] (range) (years)	33.8 ± 14.8 [30.0] (14–63)	33.6 ± 14.6 [28.5] (14–66)	33.7 ± 14.6 [30.0] (14–66)
Male, n (%)	47 (85.5)	26 (86.7)	73 (85.9)
Female, n (%)	8 (14.5)	4 (13.3)	12 (14.1)
BMI, mean ± SD [median] (range) (kg/m^2)	24.2 ± 4.4 [23.5] (16.1–37.0)	24.9 ± 4.4 [24.5] (18.9–35.1)	24.5 ± 4.4 [23.6] (16.1–37.0)
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)
Mutations, n (%)			
G11778A	37 (67.3)	20 (66.7)	57 (67.1)
T14484C	11 (20.0)	6 (20.0)	17 (20.0)
G3460A	7 (12.7)	4 (13.3)	11 (12.9)
Months since onset of vision loss, mean ± SD [median] (range)	22.8 ± 16.2 [17.8] (3–62)	23.7 ± 16.4 [19.2] (2–57)	23.1 ± 16.2 [18.2] (2–62)
Patients with onset of symptoms >1 year, n (%)	36 (65.5)	19 (63.3)	55 (64.7)
Onset of vision loss within 1 year, n (%)	19 (34.5)	11 (36.7)	30 (35.3)
Baseline logMAR distribution, n (%)			
One eye logMAR ≥1.0	5 (9.4)	2 (6.9)	7 (8.5)
Both eyes logMAR ≥1.0 (legally blind)	45 (84.9)	25 (86.2)	70 (85.4)
Both eyes logMAR <1.0	3 (5.7)	2 (6.9)	5 (6.1)
Eyes on or off-chart n (%)			

Characteristic	Idebenone (N=55) (N=53 for VA)	Placebo (N=30) (N=29 for VA)	Total (N=85) (N=82 for VA)
One eye off-chart	11 (20.8)	3 (10.3)	14 (17.1)
Both eyes off-chart	25 (47.2)	13 (44.8)	38 (46.3)
Both eyes on-chart	17 (32.1)	13 (44.8)	30 (36.6)
Patients with both eyes off-chart,* n (%)	25 (47.2)	13 (44.8)	38 (46.3)
Patients with discordant visual acuities,† n (%)	20 (37.7)	10 (34.5)	30 (36.6)
LogMAR: mean ± SD,‡ (n)			
Best eye	1.61 ± 0.64 (53)	1.57 ± 0.61 (29)	1.59 ± 0.62 (82)
Worst eye	1.89 ± 0.49 (53)	1.79 ± 0.44 (29)	1.86 ± 0.47 (82)
Both eyes	1.75 ± 0.58 (106)	1.68 ± 0.54 (58)	1.73 ± 0.57 (164)

*Off-chart defined as >logMAR 1.68 (patients unable to read any letter on the chart).
†Defined as patients with difference in logMAR >0.2 between both eyes.
‡ Applying logMAR 2.0 for counting fingers; logMAR 2.3 for hand motion; logMAR 2.6 for light perception.
Sources European Medicines Agency. Raxone® (idebenone) European Public Assessment Report. 2015;(12) Klopstock T al, 2011;(17) Klopstock T et al, 2013.(18)
Abbreviations: BMI – Body mass index; logMAR – Logarithm of the minimum angle of resolution; SD – Standard deviation; VA – Visual Acuity.

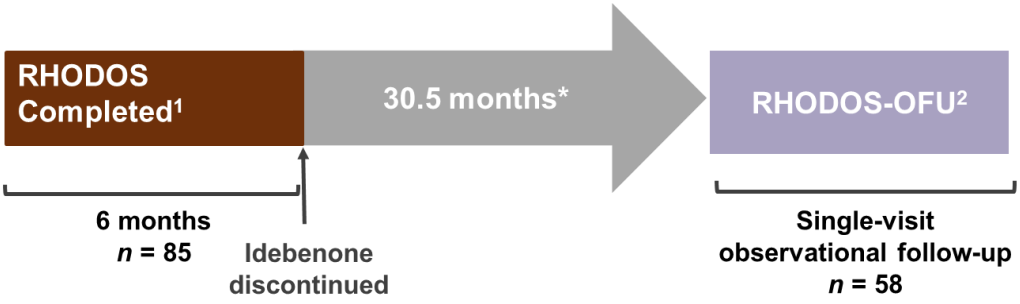
B.2.3.3 RHODOS-OFU study methodology

The RHODOS-OFU study was a long-term follow-up study, conducted to determine whether the benefits of idebenone observed in the six-month randomised period in the RHODOS trial were maintained following discontinuation of treatment.(18)

The primary objective of the study was to examine the change in VA of patients who had previously participated in the RHODOS trial, and compare the current VA with that observed at baseline and after 24 weeks of treatment in the RHODOS trial.(12,18)

During the RHODOS-OFU study period, patients were not treated with idebenone. However, there were five patients from the total efficacy population (three from the idebenone group and two from the placebo group) who reported use of idebenone between Week 24 of RHODOS and the RHODOS-OFU visit. The dose used was not provided in all cases, though three patients reported the use of 900 mg/day.(12) The design of the RHODOS-OFU trial is summarised in Figure 10.

Figure 10. RHODOS-OFU trial design



B.2.3.3.1 Eligibility criteria

The only inclusion criteria for the study was previous participation in the RHODOS trial and there were not exclusion criteria.(12)

B.2.3.3.2 Outcomes

The primary efficacy endpoint was change in best logMAR VA (best VA) compared to Visit 2/baseline and Visit 5/Week 24 or last treatment visit of RHODOS.(12)

Secondary efficacy endpoints were:

- Change in logMAR VA of individual eyes (change in VA of both eyes) compared to Visit 2/baseline and Visit 5/Week 24 or last treatment visit of RHODOS
- Change in logMAR VA of a patient's best eye (change in VA of the best eye) compared to the same eye at Visit 2/baseline or Visit 5/Week 24 or last treatment visit of RHODOS
- Change in HRQoL assessed by VF-14 questionnaire compared to Visit 2/baseline and Visit 5/Week 24 or last treatment visit of RHODOS.(12)

B.2.3.4 RHODOS-OFU study population

B.2.3.4.1 Baseline characteristics

The smaller sub-population recruited to RHODOS-OFU was representative of the RHODOS study population and there were no significant differences in the demographics or genetic characteristics of the RHODOS-OFU group compared with the original RHODOS cohort. The median time that had elapsed between Week 24 of RHODOS and the RHODOS-OFU was 30 months (range: 20.9 to 42.5 months; 131 weeks).(12,18) The details of the baseline patient characteristics in the RHODOS-OFU study are presented in

Table **8**.

Table 8. Baseline characteristics of patients in the RHODOS-OFU study

Characteristic	RHODOS-OFU Study		
	Idebenone*	Placebo*	Total
Population, n (%)	39 (73.6)†	19 (65.5)†	58 (70.7)
Age, mean ± SD‡ [median] (range) (years)	34.4 ± 15.3 [30.0] (14-63)	31.5 ± 14.2 [27.0] (14-66)	33.4 ± 14.9 [28.0] (14-66)
Male, n (%)	34 (87.2)	16 (84.2)	50 (86.2)
Months since onset of vision loss, mean ± SD‡ [median] (range)	22 ± 16 [18] (3-60)	25 ± 18 [19] (2-57)	23 ± 17 [18] (2-60)
Patients with m.11778G>A or m.3460G>A, n (%)	33 (84.6)	17 (89.5)	50 (86.2)
Onset of vision loss within 1 year, n (%)‡	16 (41.0)	6 (31.6)	22 (37.9)
Patients with both eyes off-chart, n (%)§,¶	18 (46.2)	8 (42.1)	26 (44.8)
Eyes off-chart, n (%)§,¶	44 (56.4)	19 (50.0)	63 (54.3)
LogMAR: mean ± SD			
Best eye§,¶	1.56 ± 0.70	1.51 ± 0.64	1.55 ± 0.68
Worst eye§,¶	1.89 ± 0.54	1.81 ± 0.41	1.86 ± 0.50
Both eyes§,¶	1.72 ± 0.64	1.66 ± 0.55	1.70 ± 0.61

‡At RHODOS baseline.
§For RHODOS based on efficacy population, n = 82 (53 idebenone, 29 placebo).
¶Off-chart defined as >logMAR 1.68 and applying logMAR 2.0/2.3/2.6 for counting fingers/hand motion/light perception.
Source: Klopstock T et al, 2013 (18).
Abbreviations: logMAR - Logarithm of the minimum angle of resolution; SD - Standard deviation

B.2.3.5 Expanded Access Program methodology

As described in Section B.2.3.1the RHODOS trial duration may not have been long enough to fully assess the benefit of idebenone across the trial endpoints. It is therefore important to take into account the EAP, which supported regulatory approval and demonstrated the effect of idebenone over a longer time period (treatment duration up to 36 months).

The EAP was an open-label, multicentre, retrospective, non-controlled analysis of long-term VA and safety in 111 LHON patients treated with idebenone.(19)

B.2.3.5.1 Interventions

All patients received idebenone 150 mg film-coated tablets, usually at the recommended dose of 900 mg/day. There was no control group.(12) Patient follow-up was in accordance with routine clinical practice, typically at 3-month intervals. For each participant, data on VA and AEs were collected. The best-corrected visual acuity (BCVA) was generally assessed using ETDRS logMAR charts with logMAR values or converted from standard Snellen notation to logMAR for analysis purposes.(19)

B.2.3.5.2 Eligibility criteria

Eligible patients had a confirmed mtDNA mutation and had experienced the onset of symptoms (most recent eye) within 1 year before enrolment.(19) Patients were included in the EAP from the UK, Germany, Australia, New Zealand, Poland, Sweden, Spain, Turkey, Switzerland and the United States of America.(12) The EAP was restricted to patients with an onset of vision loss of less than 12 months and therefore included a population at an earlier stage of disease progression.

B.2.3.5.3 Outcomes

The following efficacy endpoints were measured:

- CRR of VA from nadir (the point at which VA is lowest in an individual eye): VA improvement from “off-chart” to at least five letters “on-chart”, or “on-chart” improvement of at least 10 letters. The time to initial observation of a CRR was taken as the criterion for an event-based analysis, and the magnitude of recovery was reported as the best recovery observed for a patient based on the best-recovering eye.

- CRS of VA: Maintenance of VA <1.0 logMAR in those with a VA <1.0 logMAR at baseline.(19)

B.2.3.6 Expanded Access Program population

B.2.3.6.1 Baseline characteristics

Demographics of the patients enrolled in the EAP were generally representative of the disease characteristics of LHON with respect to age at onset of symptoms, mtDNA mutation and gender distribution. Table 9 shows the baseline characteristics of the efficacy population. In the EAP only patients with onset of vision loss in the second eye less than 12 months were included, compared to RHODOS where onset of visual loss due to LHON was ≤5 years.

Table 9. Patient demographics and baseline characteristics in the EAP (June 2018 cut-off)

	All	G11778A	G3460A	T14484C
Patients in the efficacy population	87/87 (100%)	54/87 (62.1%)	17/87 (19.5%)	16/87 (18.4%)
Treatment duration (months)	25.6 ± 16.9 (2.4-70.4)	24.9 ± 17.4 (3.2-70.4)	27.7 ± 16.7 (4.4-61.0)	25.5 ± 16.0 (2.4-53.8)
Gender male	71/87 (82%)	71/87 (82%)	13/17 (77%)	13/16 (81%)
Age at onset (years)	31.4 ± 17.3 (6.6-78.9)	33.3 ± 17.5 (12.1-78.9)	28.4 ± 16.8 (6.6-64.5)	28.1 ± 16.9 (8.5-56.2)
Time since onset at baseline* (months)	4.6 ± 3.0 (0.3-11.5)	4.3 ± 2.7 (0.4-11.4)	5.9 ± 3.7 (0.3-11.5)	4.4 ± 2.8 (0.9-9.3)
Interval of onset between eyes† (months)	1.7 ± 2.5 (0.0-12.6)	1.8 ± 2.5 (0.0-10.0)	1.9 ± 3.1 (0.0-12.6)	0.9 ± 1.3 (0.0-4.7)
BCVA at baseline (logMAR)	1.23 ± 0.52 (−0.18-1.8)	1.22 ± 0.59 (−0.18-1.8)	1.37 ± 0.38 (0.40-1.80)	1.12 ± 0.39 (0.28-1.80)
Baseline BCVA off-chart‡	17/87 (20%)	13/54 (24%)	3/17 (18%)	1/16 (6%)
Baseline BCVA from 1.0 to 1.68 logMAR	46/87 (53%)	25/54 (46%)	11/17 (65%)	10/16 (63%)
Baseline BCVA<1.0 logMAR	24/87 (28%)	16/54 (30%)	3/17 (18%)	5/16 (31%)

Values are given as n (%) or mean ± SD and minimum–maximum (in parentheses); percentages may not total to 100% due to rounding.
*Time since onset: time from symptoms onset to start of treatment (baseline) in the most recently affected eye. Three patients were reported by the treating physician to have one asymptomatic eye at baseline.
†Time between onset of first and second affected eye.
‡Off-chart values: not reading any letter on the ETDRS chart at 1 month (i.e., >1.68 logMAR)
Source: Catarino CB et al, 2020.(19)
Abbreviations: BCVA – Best-corrected visual acuity; logMAR – Logarithm of the minimal angle of resolution; SD – Standard deviation

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 RHODOS trial statistical analysis and definition of study groups

B.2.4.1.1 Study groups

The following populations were defined in the RHODOS trial, wherein the modified intent-to-treat (mITT) population was the primary population for the efficacy analysis and the safety population was the primary population for all safety analyses:

- Safety population (N=85; idebenone=55, placebo=30): The safety population included all randomised patients who received at least one dose of the study medication and for whom a safety assessment was available. (12)

- ITT population (N=82; idebenone=53, placebo=29): Out of the 85 patients randomised, three patients were prospectively excluded from the ITT population for all VA analyses due to inaccurate recordings in VA measurements either at baseline or at Visit 5 (Week 24). The ITT population included all randomised patients who received at least one dose of the study medication.(12)

- mITT population (N=81; idebenone=53, placebo=28): The mITT population was same as the ITT, but for VA and colour contrast analyses, one patient (randomised to placebo) who was identified as a natural history confounder due to ongoing spontaneous recovery of vision at the time of randomisation into the study population was excluded.(12)

- PP population (N=65; idebenone=41, placebo=24): All patients from the ITT population who had no major protocol deviation were included in the PP population. 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.(12)

The primary efficacy analysis was conducted in the ITT/mITT population. Where possible, results are presented for the mITT population, although for some of the secondary efficacy endpoints and post-hoc responder analyses, analyses were only performed in the ITT population. The safety analysis was conducted in the safety population.

B.2.4.1.2 Statistical methods

For continuous variables the mean, standard deviation (SD), standard error, median, and range were calculated. For discrete variables, the number of values and the percentage in each category were calculated. Analyses were performed using SAS® version 8.2. For all analyses, p-values were reported as well as two-sided 95% confidence intervals for point estimates. Statistical significance was declared for p-values below 5%. For interaction tests, a two-sided significance level of 10% was used.(12)

B.2.4.1.2.1 Primary hypothesis

The primary hypothesis was superiority of idebenone 900 mg/day over placebo in improving VF of LHON patients.(12)

B.2.4.1.2.2 Sample size and power calculation

A sample size of 84 patients was estimated based on the following assumptions for patients in the ITT population: VA change of –0.05 ± 0.3 logMAR in the placebo group and –0.25 ± 0.3 logMAR in the idebenone group. Such a difference is considered relevant from a clinical point of view (12). Under these assumptions and with the proportion of patients receiving idebenone and placebo of 2:1 respectively, 84 patients provide 80% statistical power to reject the null hypothesis of no difference in VA change between the two groups. The calculation was based on a two-sided unpaired t-test at the 5% significance level, i.e., it was performed under the additional assumption that the stratification factors do not influence the outcomes.(12)

B.2.4.1.2.3 Methods to account for missing data

Missing data were handled using a Mixed-Model for Repeated Measures (MMRM), which utilised the observed data to make inferences based on the multivariate normal distribution, with parameters estimated from the available data.(12)

B.2.4.2 RHODOS-OFU study statistical analysis and definition of study groups

B.2.4.2.1 Study groups

A total of 60 out of the 85 patients (70.6%) who participated in RHODOS were enrolled into the RHODOS-OFU study, of whom 58 patients provided VA data in both studies and were included in the analysis. 41 had previously received idebenone 900 mg/day (74.5% of idebenone-treated patients in RHODOS) and 19 had previously received placebo (63.3% of placebo-treated patients in RHODOS). Of the 60 patients, 58 (idebenone: 39 patients; placebo: 19 patients) had been included in the efficacy analysis set. Two patients were not included due to inaccurate VA assessments.(12)

B.2.4.2.2 Statistical methods

The RHODOS-OFU was an exploratory study and therefore no formal statistical hypotheses were tested.

The changes in the endpoints from baseline of RHODOS and Week 24 (or last treatment visit of RHODOS) to the present study were compared between the patients who received idebenone in RHODOS versus those who received placebo in order to explore if the difference detected in RHODOS between the groups had been maintained or not.(18) The primary endpoint was analysed using a MMRM. The model included the baseline value of RHODOS as a covariate. The response data consisted of all post-baseline visits of RHODOS (Weeks 4, 12 and 24) and of the RHODOS-OFU. The changes from baseline of RHODOS to each visit were calculated for both treatment groups of RHODOS based on the MMRM. Furthermore, the change from Week 24 of RHODOS to RHODOS-OFU as well as the changes within the treatment groups and the difference between the groups was calculated. The secondary efficacy endpoints were analysed using similar methods as used for the primary endpoint.

B.2.4.3 Expanded Access Program statistical analysis and definition of study groups

B.2.4.3.1 Study groups

Data from a total of 111 patients was collected. The following populations were defined for the analysis of safety and efficacy data:

- Safety Population (N=111): The safety population was used for analysis of safety information. It included all patients enrolled in the EAP who received at least one dose of idebenone.(19)

- Efficacy Population (N=87): The efficacy population was a sub-population of the safety population who carried one of the three major LHON-causative mtDNA mutations, who had time since onset at baseline of less than 12 months in the most recently affected eye and for whom post-baseline VA efficacy data was available.(19)

B.2.4.3.2 Statistical methods

Descriptive statistics were used to analyse safety and efficacy outcomes as there was no formal hypothesis testing. All analyses for efficacy were carried out on the efficacy population.(12,20) Descriptive statistics were applied. Continuous variables are presented as mean, SD, 95% confidence intervals, median and range where applicable.(20)

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

A complete quality assessment of the evidence informing the clinical effectiveness of idebenone is provided in Appendix D.

B.2.6 Clinical effectiveness results of the relevant studies

B.2.6.1 RHODOS trial clinical effectiveness results

The effectiveness of idebenone in recovering vision loss was consistently evident across multiple endpoints, both the primary endpoint and the key secondary endpoints, all measuring improvements in VA.(8,17)

B.2.6.1.1 Primary efficacy endpoint

B.2.6.1.1.1 Primary efficacy endpoint: best recovery of logMAR visual acuity in either right or left eye

The primary efficacy endpoint was the 'best recovery of logMAR VA between baseline and Week 24 in either right or left eye'. Based on analyses in the mITT population, idebenone was associated with numerically (logMAR −0.136 [+6 letters)) better results than placebo (logMAR −0.036 [+1 letter)) from baseline to Week 24 with regards to best recovery in VA. The difference between treatments (logMAR −0.100, equivalent to five letters) was not statistically significant.(12,40)

As described in Section B.2.3.1 (RHODOS trial methodology) ,the RHODOS trial was limited in its duration and this may have prevented differences in certain endpoints from reaching statistical significance, therefore it should be noted that although the difference in best recovery of logMAR VA between the idebenone and placebo arms was not statistically significant, this may have been because the trial did not last long enough to show a significant difference. Results for the mITT population are presented in Table 10.

Table 10. Best Recovery in visual acuity (mITT population)

	Estimated Change (95% CI) [estimated change in letters]		**Estimated Difference ± SEM (95% CI) [estimated change in letters]**	**p-value**
	Idebenone	**Placebo**		
mITT population				
N	53	28		
Week 24	−0.136 (−0.212, −0.060) [+6 letters]	−0.036 (−0.137, −0.065) [+1 letter]	−0.100 ± 0.058 (−0.214, −0.014) [5 letters]	0.0862

Source: European Medicines Agency. Raxone® (idebenone) European Public Assessment Report, 2015.(12)
Abbreviations: CI – Confidence interval; mITT – Modified intent-to-treat; SEM – Standard error of the mean.

Results for the PP population and the sensitivity analyses were consistent with those seen for the mITT population. Despite the lack of a significant difference between groups with regard to the primary endpoint, idebenone displayed an overall consistent trend of improved VA compared to placebo across secondary endpoints measuring changes in VA.(8,12)

B.2.6.1.2 Secondary efficacy outcomes

B.2.6.1.2.1 Secondary efficacy endpoint: change in best visual acuity

The change in best VA (main secondary endpoint) may be the most relevant to the impact of the disease on a patient, being the closest related to VF in daily life, a concept which was supported by the CHMP.(12) For change in best VA at 24 weeks, there was a worsening between baseline and Week 24 for patients receiving placebo (mean change logMAR 0.123, corresponding to a worsening of six letters), in contrast to a slight improvement seen in the idebenone group (mean change logMAR −0.037, corresponding to a 1-letter improvement). The difference between treatment groups (logMAR −0.160, equivalent to eight letters) favoured idebenone (p=0.015) (12,17). Results for the mITT population are presented in Table 11.

Table 11. Best visual acuity (mITT Population)

	Estimated Change (95% CI) [estimated change in letters]		**Estimated Difference ± SEM (95% CI) [estimated change in letters]**	**p-value**
	Idebenone	Placebo		
mITT population				
N	53	28		
Week 24	−0.037 (−0.123, −0.049) [+1 letter]	0.123 (0.010, 0.237) [−6 letters]	−0.160 ± 0.065 (−0.289, −0.031) [8 letters]	0.015

Source: European Medicines Agency. Raxone® (idebenone) European Public Assessment Report, 2015 (12).
Abbreviations: CI – Confidence interval; ITT – Intent-to-treat; mITT – Modified intent-to-treat; SEM – Standard error of the mean.

B.2.6.1.2.2 Secondary efficacy endpoint: change in visual acuity of the best eye at baseline and change in visual acuity for all eyes at 24 weeks

For the change in VA of best eye at baseline, idebenone was associated with better results than placebo (logMAR −0.128, equivalent to six letters; p=0.061). When data from all eyes were combined (another secondary endpoint) there was a significant difference in the mean VA between the idebenone and placebo group at 24 weeks (logMAR −0.100, equivalent to five letters; p=0.026).(8,17) Results of the secondary endpoints - change in VA of best eye and change in VA of all eyes in the ITT population are presented in

Table **12**.

Table 12. Change in visual acuity of the best eye and change in visual acuity for all eyes at 24 weeks

	Estimated Change (95% CI) [estimated change in letters]		**Estimated Difference ± SEM (95% CI) [estimated change in letters]]**	**p-value**
	Idebenone (N=53)	Placebo (N=29)		
Change in VA of the best eye at baseline				
ITT, Week 24	−0.030 (0.120, 0.060) [+1 letter]	0.098 (0.020, 0.215) [-4 letters]	−0.128 (−0.262, 0.006) [6 letters]	0.061
Change in VA for all eyes				
ITT, Week 24	−0.054 (−0.114, 0.005) [+ 2 letters]	0.046 (−0.032, 0.123) [-2 letters]	−0.100 (−0.188, −0.012) [5 letters]	0.026

Sources: Klopstock T et al, 2011; Santhera Pharmaceuticals AG. Idebenone (Raxone) NCPE Submission, 2017 (8,17).
Abbreviation: CI – Confidence interval; ITT – Intent-to-treat; SEM – Standard error of the mean.

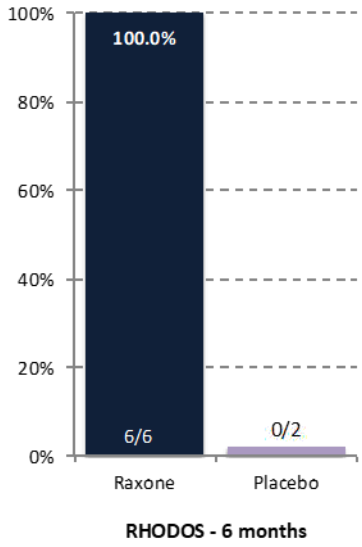
B.2.6.1.2.3 Secondary efficacy endpoint: count of eyes/patients for which the visual acuity improves (at least 0.2 logMAR) between baseline and Week 24

There was a higher proportion of patients/eyes in the idebenone group compared to the placebo group with an improvement in VA of at least logMAR 0.2 at Week 24 compared to baseline. In analyses on the primary endpoint in the mITT population, 20 out of 53 patients in the idebenone arm had a VA improvement (37.7%) compared to 6 out of 28 patients in the placebo arm (21.4%). Similarly, 30 out of 106 eyes (28.3%) in the idebenone arm had VA improvement compared to 8 out of 56 eyes (14.3%) in the placebo arm. The difference between the treatment arms were not statistically significant.(12)

B.2.6.1.2.4 Secondary efficacy endpoint: clinically relevant stabilisation of residual visual acuity below 1.0 logMAR

Treating patients with idebenone at an early stage, where VA is preserved in at least one eye, can potentially prevent patients from becoming blind. This was demonstrated by the analysis of the pre-specified secondary endpoint in RHODOS 'the proportion of patients with at least one eye ≤0.5 logMAR at baseline in which the VA in the initially least affected eye does not deteriorate to logMAR 1.0 or more'. None of the six patients in the idebenone group showed deterioration to logMAR 1.0 or more whereas both patients in the placebo group showed such deterioration (0% in placebo vs. 100% in idebenone, p=0.036) (8,12) as shown in Figure 11, however, the small sample size is noted (n=8).

Figure 11. Proportion of patients in RHODOS with visual acuity of ≤ 0.5 logMAR at baseline who did not deteriorate to ≥1.0 logMAR at last assessment



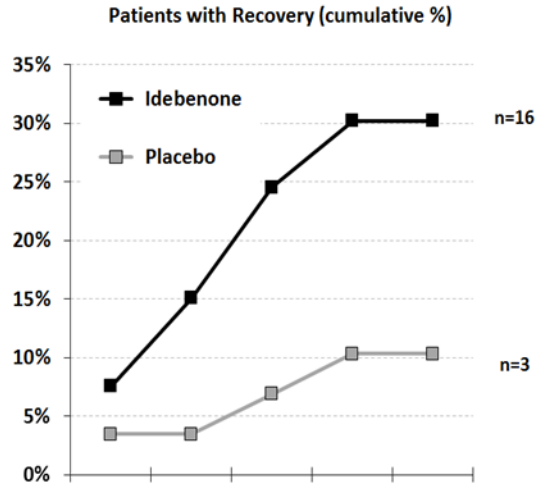
Source: Santhera Pharmaceuticals AG. Idebenone (Raxone) NCPE Submission, 2017.(8)

B.2.6.1.2.5 Secondary efficacy endpoint: clinically relevant recovery

A post-hoc responder analysis of CRR was also conducted, which was considered by the CHMP to be a valuable marker for assessing treatment benefit.(12) CRR was defined as either moving from 'off-chart' VA to being able to read at least 5 letters on the chart or the ability to read at least 10 additional letters on the chart.(10) A higher proportion of patients in the idebenone group (ITT: 30.2%; n=16) than in the placebo group (ITT: 10.3%, n=3) showed CRR from baseline (p= 0.056). CRR of vision was seen in idebenone-treated patients up to ~4 years from onset of disease (

Figure **12**), which is consistent with the observation that in LHON affected RGCs can remain “inactive but viable” allowing recovery of vision for several years before they are lost.(8,40,48)

Figure 12. Clinically relevant recovery (cumulative CRR) in RHODOS



Disease Duration [years]*	≤ 1	>1 - 2	>2 - 3	>3 -4	> 4 - 5	total	% Recovery
Idebenone Recovery (n)	4	4	5	3	0	16	30.2%
N per Group	19	13	11	5	5	53	
Placebo Recovery (n)	1	0	1	1	0	3	10.3%
N per Group	10	6	5	4	4	29	

*Disease duration at baseline assessment
Source Santhera Pharmaceuticals AG. Idebenone (Raxone) NCPE Submission, 2017 (8)
Abbreviation: CRR – Clinically relevant recovery

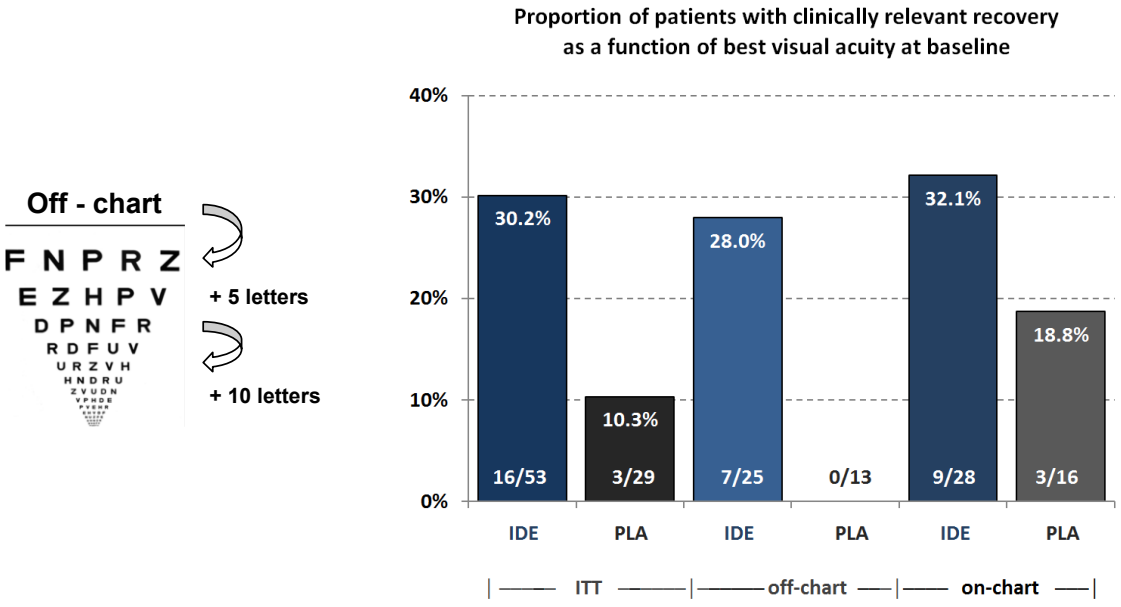
B.2.6.1.2.6 Responder analysis for patients “off-chart” at baseline

Patients who were “off-chart” at baseline comprised a subgroup of severely affected patients who were unable to read any letters on the chart. In this subgroup, 28% (7 of 25 patients) of the idebenone-treated patients were able to read at least one full line (5 letters) on-chart at Week 24, whilst none of the 13 patients in the placebo arm recovered to this level of vision (p=0.0722). Applying the same analysis to all eyes instead of patients resulted in a significant difference between idebenone responders and placebo responders (p=0.0078).(8,12)

Both “off-chart” and “on-chart” patients at baseline experienced a higher rate of CRR in the idebenone-treated arm compared to placebo. The details are presented in

Figure **13**.

Figure 13. Proportion of patients in RHODOS with CRR as a function of VA at baseline



Abbreviations: CRR – Clinically relevant recovery; Ide – Idebenone; ITT – Intent-to-treat; Pla – Placebo; VA – Visual acuity

B.2.6.1.2.7 Secondary efficacy endpoint: proportion of patients and eyes with clinically relevant recovery from the visual acuity nadir

A comparison of the proportions of idebenone and placebo-randomised patients in the mITT population who recovered from their VA nadir is presented in

Table **13**. A statistically significant difference was observed between the proportions of patients who recovered from their VA nadir in each treatment arm in favour of idebenone (p=0.0321). Statistical significance was also reached in patients with a disease duration ≥1 year, but there was no significant between treatment difference for disease duration <1 year. Amongst the three mtDNA mutations, a significant difference in favour of idebenone was only seen in the subgroup with the G11778A mtDNA mutation. CRR from VA nadir was seen in 23 eyes (21.7%) for patients in the idebenone group and in three eyes (5.4%) for patients in the placebo group. This difference was statistically significant in favour of idebenone (p=0.0066).(12)

Table 13. Proportion of patients with clinically relevant recovery from nadir at Week 24 (mITT population)

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

Source: European Medicines Agency. Raxone® (idebenone) European Public Assessment Report, 2015 (12).
Abbreviations: LHON – Leber's hereditary optic neuropathy; mtDNA – Mitochondrial deoxyribonucleic acid

B.2.6.1.2.8 Secondary efficacy endpoint: time to clinical relevant recovery

A logrank test of the difference in the median time to recovery since disease onset in the mITT population between the idebenone-treated (42.4 months) and placebo-treated (median not reached) patients demonstrated a statistically significant difference between the groups (p=0.0133) in favour of idebenone.(12)

B.2.6.1.2.9 Discordant VA at baseline

A post-hoc subgroup analysis was performed in 30 patients with discordant VA (i.e. patients with difference of logMAR >0.2 between eyes) at baseline. A formal test of interaction between the effect of idebenone and discordance of VA at baseline was significant for the secondary endpoints: best recovery in VA (estimated mean difference: logMAR −0.285; p=0.011), change in best VA (estimated mean difference: logMAR −0.421; p=0.003), change in VA of the best eye at baseline (estimated mean difference: logMAR −0.415; p=0.003) and change in VA for all eyes (estimated mean difference: logMAR −0.348; p=0.0001) when compared with placebo.(17)

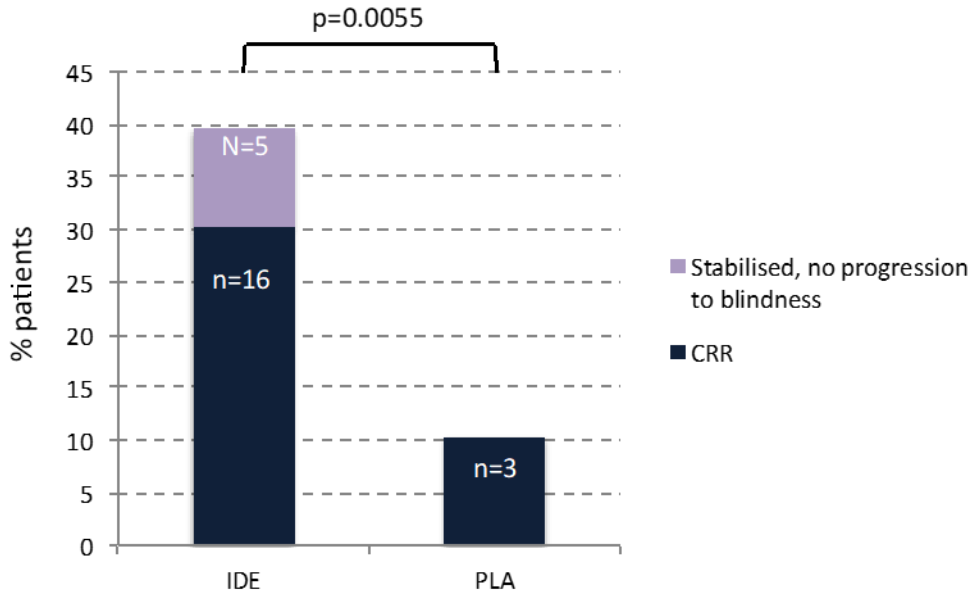
The trend towards improvement with idebenone was also apparent in a responder analysis. For patients with discordant visual acuities at baseline, there was a 45% difference in the responders for the best recovery of VA (p=0.024); and a 32.5% difference in the endpoint assessing the change in VA for all eyes (p=0.011). Although subgroup analysis should be interpreted with caution, subdividing patients into those with and without discordant interocular visual acuities indicated that patients with discordant eyes had the largest treatment effect.(17)

B.2.6.1.2.10 Composite analysis of disease progression in RHODOS ITT

Response to therapy in LHON may either be observed as a 'recovery' or 'stabilisation' of VA. Recovery of vision is easier to be detected where significant vision loss has already occurred. Conversely in those with a relatively preserved VA, detection of recovery is less likely, and stabilisation in VA is a clinically meaningful outcome (Section B.1.3.4, Figure 5). Therefore, to determine the overall benefit, i.e, CRB of idebenone on disease progression across the spectrum of vision loss, a composite post-hoc analysis was carried out. In this analysis, the overall benefit (CRB) was defined as either achieving a CRR (clinically relevant response of two lines improvement or one line if off-chart at baseline) or a clinically relevant stabilisation (patients with logMAR ≤0.5 at baseline that did not deteriorate to blindness, i.e. remained at logMAR<1 in at least one eye).(8)

The analysis demonstrated a significant overall benefit with idebenone compared with placebo. It was found that 21 of 53 patients in the idebenone arm (39.6%) experienced either a CRR or CRS compared to 3 of 29 in the placebo arm (10.3%; p=0.0055) (8,48). The details are presented in Figure 14.

Figure 14. Composite analysis of disease progression in RHODOS



Source: Santhera Pharmaceuticals AG. Idebenone (Raxone) NCPE Submission, 2017 (8).
Abbreviations: CRR – clinically relevant recovery; IDE – idebenone; PLA – placebo.

B.2.6.1.2.11 Secondary efficacy endpoint: change in health-related quality of life

Only small changes in the VF-14 score were observed over the 24-Week study period and at Week 24, there was no significant difference between the treatments (estimated mean treatment difference -1.37; 95% CI: -6.25, 3.51; p=0.577).(12)

At Week 24, 12 patients (22.6%) in the idebenone group and 7 patients (24.1%) in the placebo group from the ITT population had an improvement in CGIC. A total of 43 patients (81.1%) in the idebenone group and 24 patients (82.8%) in the placebo group were experiencing less fatigue or no change in fatigue levels.(12)

At Week 24, patients in both treatment groups reported minimally elevated energy levels assessed by VAS score (0.37 mm for idebenone and 2.17 mm for placebo) with no statistically significant difference between the treatment groups (-1.80; 95% CI: -11.37, 7.77; p=0.709).(12) As described in Section B.2.3.1 and ratified by clinical experts,(26) the RHODOS trial was limited by a 24-Week duration, which may not have been long enough to show the treatment benefit of idebenone. This may explain why no statistically significant difference in VF-14 score was observed.

B.2.6.1.2.12 Secondary efficacy endpoint: colour contrast sensitivity

A colour contrast sensitivity test was performed on a subset of patients in one study centre. Most patients (92%) had abnormal colour contrast sensitivity at baseline in both protan and tritan domains in both eyes. There was a significant improvement in the tritan colour contrast in the idebenone group at 12 weeks (difference between groups: -14.51%; 95% CI: -24.19 to -4.83; p=0.004) and 24 weeks (difference between groups: -13.63%; 95% CI: -23.61 to -3.66; p=0.008). A similar trend was observed in the protan domain, but this did not reach statistical significance.(17)

B.2.6.1.2.13 Secondary efficacy endpoint: change in scotoma area

Change in scotoma area was assessed by Humphrey™ 24:2 visual field analysis. However, the interpretation of these visual field data across the entire study population was difficult due to the unreliability of the assessments caused by false positive/negative errors and fixation losses.(12)

B.2.6.1.2.14 Secondary efficacy endpoint: change in retinal nerve fibre layer thickness

There was no difference in the pattern of RNFL thickness at baseline for patients grouped by disease onset of ≤6 months, 6 months to 1 year, and >1 year. Consistent with the VA data, there was a trend towards maintaining RNFL thickness in the idebenone group in superior, nasal and inferior quadrants, among patients with ≤6 months disease history. Due to the small sample size, no formal statistical analysis was conducted.(17)

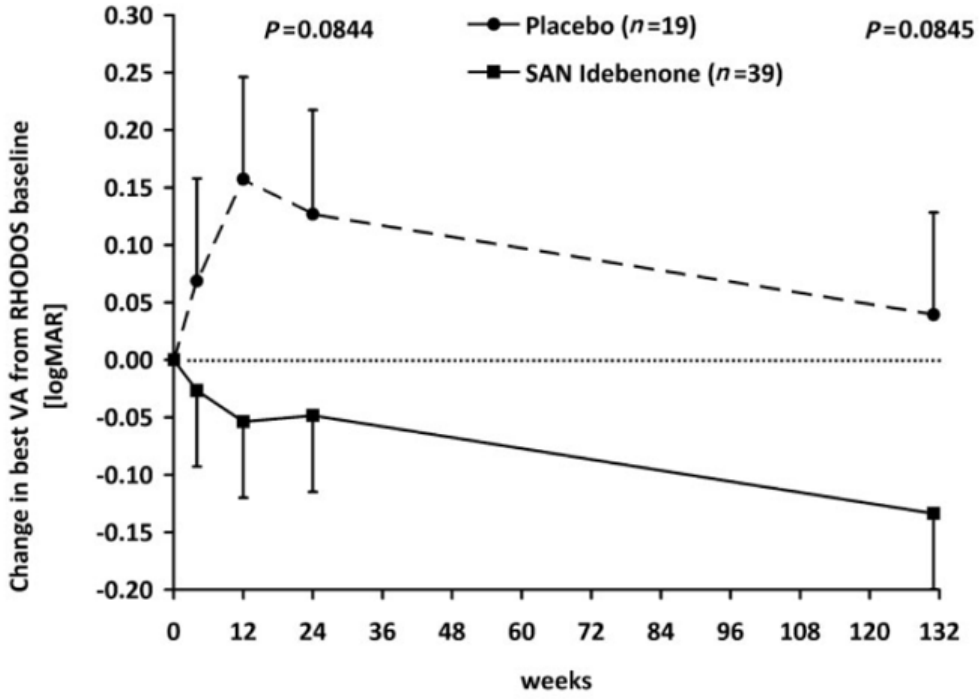
B.2.6.2 RHODOS-OFU study clinical effectiveness results

B.2.6.2.1 B.2.6.2.1 Primary efficacy endpoint

B.2.6.2.1.1 Primary efficacy endpoint: change in best visual acuity

Best VA at the RHODOS-OFU visit at Week 132 was slightly worse than at baseline in patients in the placebo group (mean change in logMAR +0.039, corresponding to a worsening of one letter) whereas best VA improved in the idebenone group (mean change in logMAR -0.134, corresponding to an improvement of six letters).(12,40) The benefit of idebenone was maintained in this off-medication period (i.e. after Week 24 of the RHODOS trial) with a difference of logMAR −0.173 (8 letters); p=0.0845 between treatment groups from baseline in RHODOS to RHODOS-OFU favouring idebenone (Figure 15).(8,18)

Figure 15. Change in visual acuity over time for the best visual acuity (logMAR)



Data are estimated means ± SEM from MMRM, based on the change from baseline (in weeks) and plotted for the two treatment groups as defined in the RHODOS study. No treatment was given between Week 24 and Week 131. Worsening/improvement of visual acuity is indicated as positive/negative values in change of logMAR. A difference of logMAR 0.1 corresponds to five letters or one line on the Early Treatment Diabetic Retinopathy Study chart. The P-values are given for the difference between treatment groups.
Source: Klopstock T et al, 2013 (18)
Abbreviations: logMAR – Logarithm of the minimum angle of resolution; MMRM – Mixed-model of repeated measures; SEM – Standard error of the mean; VA – Visual acuity

The estimated difference between groups for the entire study period (i.e. RHODOS baseline to RHODOS-OFU visit) was comparable to that from RHODOS baseline to Week 24 (logMAR −0.173 versus −0.175), indicating that the treatment effect of idebenone was maintained long after therapy was terminated.(18,40,41) Both treatment groups showed almost identical improvements in best VA between Week 24 of RHODOS and the RHODOS-OFU visit (idebenone: logMAR −0.085, placebo: logMAR −0.088, both equivalent to improvement by four letters). A summary of the mean change in best VA from baseline of RHODOS to Week 24 and to the RHODOS-OFU visit, and the change from Week 24 to the RHODOS-OFU visit are provided in Table 14.(12)

Table 14. Change in best visual acuity in RHODOS and RHODOS-OFU (total efficacy population)

Change in best VA	Estimated Change* (95% CI) [estimated change in letters]		Estimated Difference* ± SEM (95% CI) [difference in letters]	p-value
	Idebenone in RHODOS	Placebo in RHODOS	Idebenone vs. Placebo	
N	39	19		
Between baseline† and Week 24[2]	−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
Between baseline† and OFU visit	−0.134 (−0.265, −0.003) [+6 letters]	0.039 (−0.136, 0.215) [−1 letter]	−0.173 ± 0.100 (−0.370, 0.024) [8 letters]	0.0845
Week 24† and OFU‡ visit	−0.085 (−0.195, 0.024) [+4 letters]	−0.088 (−0.246, 0.071) [+4 letters]	0.002 ± 0.098 (−0.190, 0.195) [0 letters]	0.9819

*Data is estimated mean calculated from MMRM.
†Baseline and Week 24 in RHODOS.
‡RHODOS-OFU study - SNT-II-003-OFU (median time since Week 24 of RHODOS was 30 months).
Sources: European Medicines Agency. Raxone® (idebenone) European Public Assessment Report, 2015 (12); Klopstock T et al, 2013 (18).
Abbreviations: CI – Confidence interval; MMRM – Mixed-model of repeated measures; OFU – Observational follow-up study; SEM – Standard error of the mean; VA – Visual acuity.

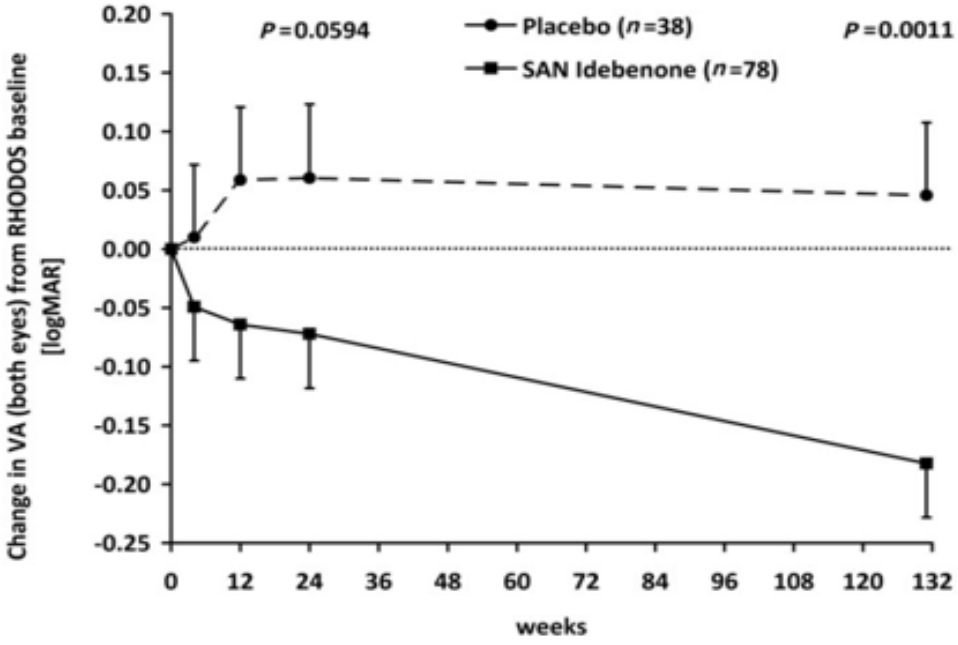
The influence on the VA outcome was also investigated for the five patients who received idebenone in the follow-up period (outside protocol, three from the idebenone group and two from the placebo group) (see Section B.2.3.3). The change in best VA from Week 24 to the RHODOS-OFU visit was comparable to that seen in the subgroup in which idebenone-treated patients were excluded.(18)

B.2.6.2.2 Secondary efficacy endpoints

B.2.6.2.2.1 Secondary efficacy endpoint: change in visual acuity of both eyes and change in visual acuity of the best eye

For the secondary VA endpoints (change in VA of both eyes and in patient's best eye), broadly similar results were obtained.(12) The mean change in VA of individual eyes from baseline of RHODOS to the RHODOS-OFU study visit at Week 132 showed a statistically significant difference between treatment groups in favour of the idebenone group (logMAR −0.228 [+11 letters]; p=0.0011).(18) The change in VA of both eyes is presented in Figure 16.

Figure 16. Change in visual acuity of both eyes



Data are estimated means ± SEM from MMRM, based on the change from baseline (in weeks) and plotted for the two treatment groups as defined in the RHODOS study. No treatment was given between Week 24 and Week 131. Worsening/improvement of visual acuity is indicated as positive/negative values in change of logMAR. A difference of logMAR 0.1 corresponds to five letters or one line on the Early Treatment Diabetic Retinopathy Study chart. The P-values are given for the difference between treatment groups.
Source: Klopstock T et al, 2013 (18)
Abbreviations: logMAR – Logarithm of the minimum angle of resolution; MMRM – Mixed-model of repeated measures; SEM, – Standard error of the mean; VA – Visual acuity

B.2.6.2.2.2 Secondary efficacy endpoint: change in HRQoL assessed by VF-14 questionnaire

VF-14 data were available for 57 patients enrolled in RHODOS-OFU. The change in HRQoL was assessed using the VF-14 questionnaire which was compared to visit 2/baseline and visit 5/week24 or last treatment visit of RHODOS.(12) Overall, the changes between VF-14 recorded during RHODOS and RHODOS-OFU were small and differences between idebenone and placebo groups were not statistically significant. There was a slight worsening in the HRQoL in the idebenone group (−1.7%) compared to a small improvement in the placebo group (2.4%; p=0.205) for the entire period between RHODOS baseline to RHODOS-OFU.(12)

B.2.6.2.2.3 Other efficacy endpoint: best recovery of visual acuity

For the analysis of best recovery of VA, there was a logMAR −0.147 (seven letters, p=0.004) improvement in the idebenone group and logMAR −0.054 (two letters, p=0.459) improvement in the placebo group between Week 24 of RHODOS and the RHODOS-OFU visit. The difference between treatment groups for the entire study period from baseline of RHODOS to the RHODOS-OFU visit was logMAR −0.158 (p=0.086).(18,40,41)

B.2.6.2.2.4 Other efficacy endpoint: clinically relevant recovery rates

Treatment benefits of the idebenone recipients who were ‘off-chart’ at RHODOS baseline and achieved CRR at Week 24 were maintained at the RHODOS-OFU visit.(18,40) Responder analysis in the RHODOS trial previously showed that for patients with ‘off-chart’ VA in both eyes at baseline, none of the 13 patients in the placebo group but seven out of 25 patients in the idebenone group had improved to reading at least a full line at Week 24 (p=0.07) (8,17,18) (see Section B.2.6.1). The long-term persistence benefit of the idebenone treatment effect was maintained for all five patients who participated in the RHODOS-OFU study, even after discontinuing treatment at 24 weeks. This benefit remained stable compared to the placebo group during the 2.5-years (30 months) non-treatment observation period, confirming idebenone’s sustained treatment benefit.(8,18)

In a subgroup of 63 patient eyes that were ‘off-chart’ at baseline, rates of CRR were significantly higher with idebenone than with placebo at the follow-up visit (40.9 % vs. 10.5 % of eyes; p=0.02).(18,40,41)

B.2.6.3 Expanded Access Programme clinical effectiveness results

B.2.6.3.1 Clinically relevant recovery in visual acuity from nadir

Of the 87 patients, 40 patients (46.0%) (by eyes, 67/173; 38.7%) had a CRR from nadir to the last observation visit (Table 15).

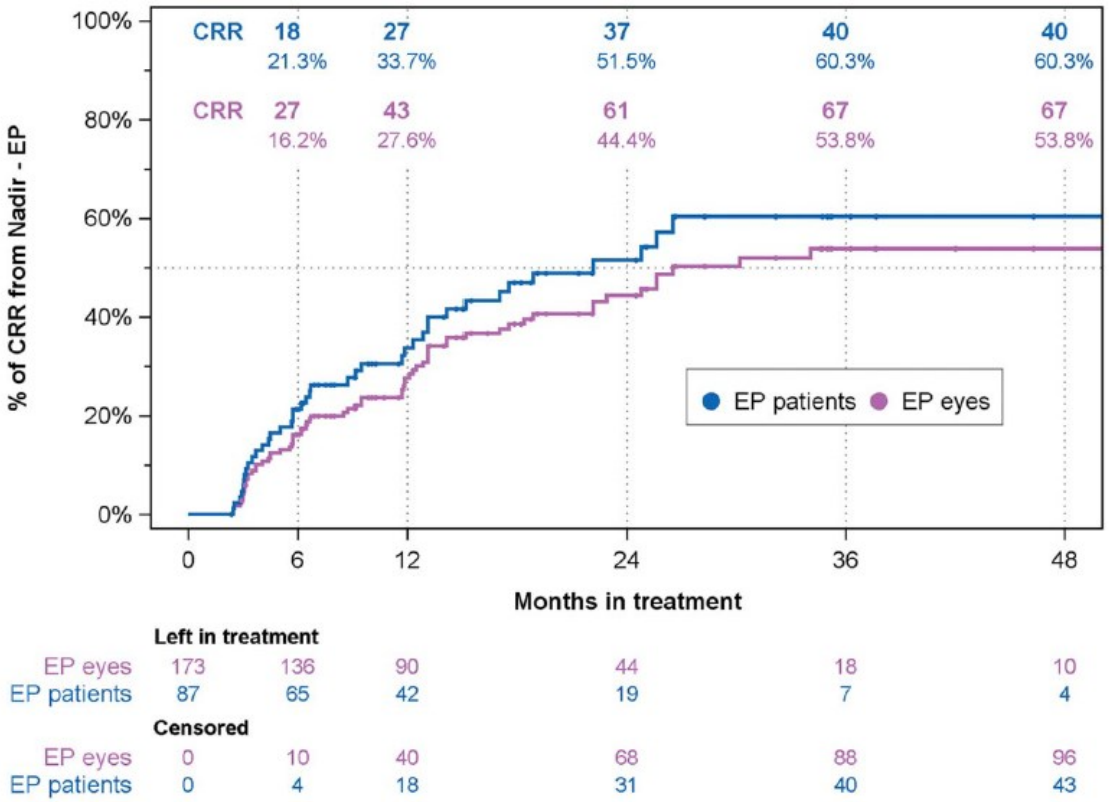
Table 15. Patients with clinically relevant recovery from nadir

	All	G11778A	G3460A	T14484C
Best recovery of VA: Patients with a CRR*	40/87 (46.0%)	21/54 (39%)	7/17 (41%)	12/16 (75%)
Time to an initial CRR [months]	9.5 ± 7.0 (2.5-26.5)	11.2 ± 7.8 (2.5-26.5)	7.3 ± 3.4 (2.5-12.9)	7.8 ± 6.8 (3.0-25.6)
Magnitude of recovery at initial CRR				
logMAR	0.45 ± 0.31 (0.20-1.62)	0.39 ± 0.32 (0.20-1.62)	0.39 ± 0.20 (0.22-0.76)	0.60 ± 0.30 (0.22-1.20)
No. of letters ETDRS	22 ± 15 (10-81)	19 ± 16 (10-81)	19 ± 10 (11-38)	30 ± 15 (11-60)
Magnitude of recovery at last observation				
logMAR	0.72 ± 0.46 (0.20-1.80)	0.52 ± 0.39 (0.20-1.76)	0.61 ± 0.31 (0.24-1.10)	1.12 ± 0.40 (0.46-1.80)
No. of letters ETDRS	36 ± 23 (10-90)	26 ± 19 (10-88)	30 ± 15 (12-55)	56 ± 20 (23-90)

Values are given as n (%) or mean ± SD and minimum–maximum (in parentheses); percentages may not total to 100% due to rounding.
*CRR is improvement from an off-chart best VA to on-chart by the equivalent of at least one full line on an ETDRS chart (5 letters) or an improvement in an on-chart best VA by the equivalent of at least two lines (10 letters).
Source: Catarino CB *et al.* 2020 (19).
Abbreviations: CRR – Clinically relevant recovery; ETDRS – Early Treatment Diabetic Retinopathy Study; logMAR – Logarithm of the minimal angle of resolution; SD – Standard deviation

The proportion of eyes with a CRR is lower than the proportion of patients with a CRR because not all patients experienced recovery in both eyes. Time to initial observation in patients with a CRR varied between 2.5 and 26.5 months, with a mean of 9.5 months (Figure 17).(19)

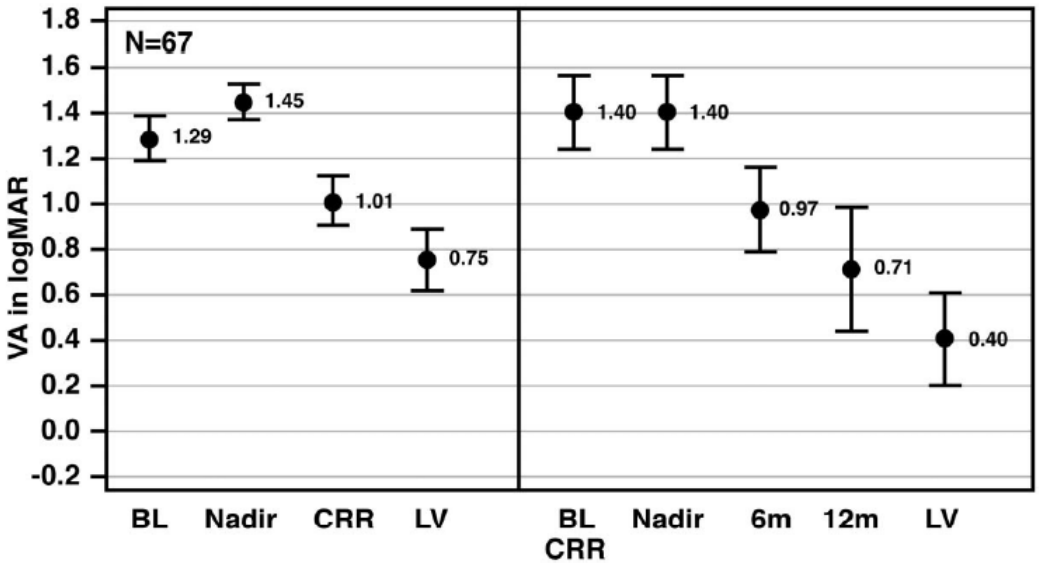
Figure 17. Kaplan Meier curves of clinically relevant recovery



Cumulative percentage of total number of patients and eyes, respectively, with a CRR, as a function of treatment duration, in the efficacy population.
Source: Catarino CB et al, 2020 (19).
Abbreviations: CRR – Clinically relevant recovery; EP – Efficacy population

The average magnitude of recovery, defined based on a patient's best-recovering eye, amounted to 22 letters (0.45 logMAR) on the ETDRS chart at the initial observation of CRR and increased with prolonged treatment to 36 letters (0.72 logMAR) at the last observation (Table 15), i.e. reaching more than seven lines, far in excess of the minimum threshold of 10 letters, the criterion for CRR (Table 15). This increase of the magnitude of response with longer treatment duration was confirmed when the magnitude of CRR was analysed specifically in 22 eyes that had demonstrated a CRR by 6 months and for which follow-up data of 12 months or longer were available (Figure 18, right). Eyes that eventually achieved a CRR and VA improvement, showed some degree of transient deterioration into a nadir, despite the start of treatment. Later, these eyes showed a CRR regardless of VA category achieved at nadir (Figure 18, left). A treatment duration of at least 18–24 months is needed to maximize the probability of CRR because a certain degree of transient deterioration to a nadir may occur despite therapy initiation and continued treatment after an initial CRR provides further benefit.(19) This was also demonstrated in the LEROS trial, in which patients were treated with idebenone over the course of 24 months and showed CRR in 41.3% of idebenone-treated eyes, compared to 20.7% of natural history-matched eyes (see Appendix M).

Figure 18. Magnitude of mean best-corrected visual acuity recovery over the course of time in eyes with a CRR



Left: Average BCVA observed at BL, nadir, initial observation of CRR, and at the LV for all eyes that experienced a CRR (n=67). Right: Improvement of BCVA over the course of time, at given treatment durations, in those eyes that experienced a CRR within 6 months of treatment initiation and where follow-up data were available (n=22). All mutations. All off-chart VA values were imputed to 1.8 logMAR. Error bars indicate the 95% CI.
Source: Catarino CB et al, 2020 (19).
Abbreviations: BCVA – Best-corrected visual acuity; BL – Baseline; CI – Confidence interval; CRR – Clinically relevant recovery; logMAR – Logarithm of the minimal angle of resolution; LV – Last observation visit; VA – Visual acuity

For 173 eyes in 87 patients (one patient's eye had vision loss attributed to another ocular pathology), 86 (49.7%) were off-chart at nadir; 76 (43.9%) had a best VA between 1.0-1.68 logMAR; and 11 (6.4%) had a best VA below 1.0 logMAR. For eyes that at nadir were off-chart, 24.4% had a CRR and 53.9% of those between 1.0-1.68 logMAR and 45.5% of those below 1.0 logMAR at nadir showed CRR (Table 16).(19)

Table 16. Clinically relevant recovery by individual eyes as a function of best-corrected visual acuity at nadir (Data cut-off June 2018)

VA Category at Nadir	Eyes	Eyes with a CRR* within category	Eyes with a CRR and BCVA [logMAR] at the last observation		
			BCVA >1.0	>0.5 BCVA <1.0	BCVA ≤0.5
Off-chart	86/173 (49.7%)	21/86 (24%)	14	2	5
From 1.0 to 1.68 logMAR	76/173 (44%)	41/76 (54%)	12	13	16
Below 1.0 logMAR	11/173 (6%)	5/11 (46%)	NA	0	5
All†	173/173 (100%)	67/173 (39%)	26	15	26

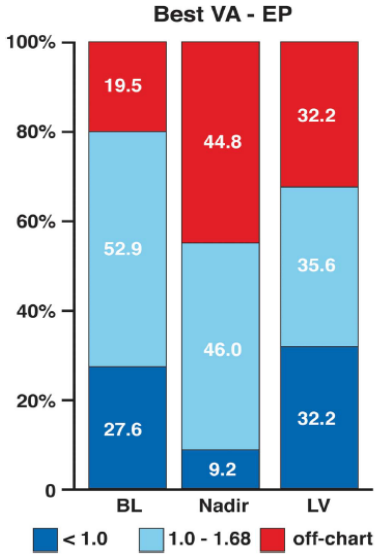
Values are given as n (%); Percentages may not total to 100% due to rounding.
*CRR is improvement from an off-chart BCVA to on-chart by the equivalent of at least one full line on an ETDRS chart (5 letters) or an improvement in an on-chart BCVA by the equivalent of at least two lines (10 letters) at LV.
†One patient had vision loss in one eye not related to LHON.
Source: Catarino CB et al, 2020 (19).

Abbreviations: BCVA – Best-corrected visual acuity; CRR – Clinically relevant recovery; LHON – Leber's hereditary optic neuropathy; logMAR – Logarithm of the minimal angle of resolution; LV – Last observation visit; VA – Visual acuity

Visual outcomes were markedly improved compared to nadir, with more than a tripling of patients with a BCVA <1.0 logMAR from nadir (9.2%) to the last observation visit (32.2%) and a reduction in off-chart patients (44.8% to 32.2%). The overall outcome resulting from the shift of patients across BCVA categories is visualized in

Figure 19.(19)

Figure 19. Shift of patients, over the course of treatment time, across categories of best-corrected visual acuity



Efficacy population, n=87. Bar chart for distribution of patients based on categories for BCVA at BL, at nadir, and at the LV mutations.
Source: Catarino CB et al, 2020 (19).
Abbreviations: BCVA – Best-corrected visual acuity; BL – Baseline; EP – Efficacy population; LV – Last observation visit; VA – Visual acuity.

B.2.6.3.2 Clinically relevant stabilisation of visual acuity

In the efficacy population, 24 of the 87 subjects had a BCVA at baseline <1.0 logMAR in at least one eye, 50% (12/24) of whom experienced CRS (Table 9 and Table 17). For patients with CRS, the mean BCVA improved from 0.47 logMAR at baseline to 0.29 logMAR at the last visit, corresponding to nine letters on the ETDRS chart. Thus, compared with the natural disease course, early idebenone treatment provides an opportunity to prevent severe vision loss over a timespan when further BCVA deterioration would be expected for most patients (19).

Three patients had one unaffected eye at baseline, out of which one patient deteriorated to an off-chart BCVA in both eyes after 6 months of therapy, with no recovery at the visit. However, both the other patients maintained unaffected vision in the unaffected eye at the last visit after 12 months' follow-up. These two patients also had a CRR in the fellow eye, which had presented with a BCVA worse than 1.0 logMAR at start of treatment (19).

Table 17. Clinically relevant stabilisation for the subset of patients with best-corrected visual acuity at baseline <1.0 logMar

	All	G11778A	G3460A	T14484C
BCVA stabilisation: Patients with CRS*	12/24 (50%)	7/16 (44%)	1/3 (33%)	4/5 (80%)
BCVA at baseline (logMAR)	0.47 ± 0.36 (−0.18-0.96)	0.31 ± 0.34 (0.18-0.88)	0.94	0.62 ± 0.28 (0.28-0.96)
BCVA at last observation (logMAR)	0.29 ± 0.29 (−0.16-0.8)	0.35 ± 0.34 (−0.16-0.8)	0.34	0.17 ± 0.29 (−0.14-0.42)
Treatment duration (months)†	30.1 ± 19 (9.9-67.8)	25.5 ± 20.6 (10.7-67.8)	40.0	35.8 ± 18.6 (9.9-53.8)

Values are given as n (%) or mean ± SD and minimum–maximum (in parentheses); Percentages may not total to 100% due to rounding.
*CRS: BCVA had to be maintained in an eye with BCVA ,1.0 logMAR at start of the treatment.
†Calculations only consider patients with CRS (12 patients).
Source: Catarino CB et al, 2020 (19).
Abbreviations: BCVA – Best-corrected visual acuity; CRS – Clinically relevant stabilisation; logMAR – Logarithm of the minimal angle of resolution; SD – Standard deviation.

B.2.7 Subgroup analysis

A subgroup analysis of data from the RHODOS trial has been carried out to provide additional information on the effect of idebenone on VA in the subgroup of patients with logMAR <1 at baseline compared to patients with logMAR ≥1. This analysis, however, should be interpreted with caution due to small patient numbers in the logMAR <1 subgroup in the RHODOS study.

In the analysis of the primary outcome (Best recovery in VA; Table 18) the test for interaction between the logMAR <1 group and the logMAR ≥1 group was not significant. As discussed in Section B.2.3.1, the primary endpoint analysis has some inherent limitations, specifically in a patient population in which the worst eye is already off-chart and further deterioration may not be possible. In such a population, a worsening of the best eye is not accounted for, as the "least worsening" would be in the worst eye by simply remaining at the same level. Therefore, this comparative subgroup analysis is considered inappropriate to assess whether the patients can retain vision in their best eye. The change in best VA (main secondary outcome) may be the most relevant to the impact of the disease on a patient, being the closest related to VF in daily life.

Table 18. Primary outcome efficacy results (RHODOS)

	Estimated Change (95% CI) [estimated change in letters]		**Estimated Difference ± SEM (95% CI) [estimated change in letters]**	**p-value**
	Idebenone	**Placebo**		
Primary endpoint: Best Recovery in VA				
ITT, n	53	29		
ITT, 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
Subgroup: Best eye LogMAR <1 at baseline, n	8	4		
Subgroup: Best eye LogMAR <1 at baseline, Week 24 (MMRM)	-0.119	-0.151	0.033	0.936
Subgroup: Best eye LogMAR >=1 at baseline, n	45	25		
Subgroup: Best eye LogMAR >=1 at baseline, Week 24 (MMRM)	-0.131	-0.074	-0.059	0.334
Test for interaction (3-way)				0.5346

Abbreviations: CI – Confidence interval; logMAR - Logarithm of the minimal angle of resolution; MMRM – Mixed-model repeat measures; SEM – Standard error of mean; VA – Visual acuity

Analysis of the secondary outcomes by subgroup (Table 19 to Table 21) shows there is a difference in the treatment effect in these subgroups. For the most clinically relevant main secondary endpoint, change in best VA, (17) the magnitude of the treatment effect in the logMAR <1 was far greater than in the logMAR ≥1 group (-0.976 vs. -0.063). Similarly, the magnitude of treatment effect in the secondary endpoint of change in VA of best eye at baseline was greater in the logMAR <1 group (-1.014 vs -0.061). For both endpoints the test for interaction test was statistically significant.

Table 19. Main secondary outcome efficacy results (RHODOS*)*

	Estimated Change (95% CI) [estimated change in letters]		**Estimated Difference ± SEM (95% CI)** [estimated change in letters]	**p-value**
	Idebenone	**Placebo**		
Key secondary endpoint: Best VA at Week 24 (best eye at Week 24) compared to best VA at Baseline (best eye at Baseline)				
ITT, n	53	29		
ITT, 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
Subgroup: Best eye LogMAR <1 at baseline, n	8	4		
Subgroup: Best eye LogMAR <1 at baseline, Week 24 (MMRM)	-0.3883	0.5875	-0.9757	0.0754
Subgroup: Best eye LogMAR >=1 at baseline, n	45	25		
Subgroup: Best eye LogMAR >=1 at baseline, Week 24 (MMRM)	-0.0503	0.0124	-0.0627	0.2964
Test for interaction (3-way)				0.0667

Abbreviations: CI – Confidence interval; logMAR - Logarithm of the minimal angle of resolution; MMRM – Mixed-model repeat measures; SEM – Standard error of mean; VA – Visual acuity

Table 20. Main secondary outcome efficacy results (RHODOS)

	Estimated Change (95% CI) [estimated change in letters]		**Estimated Difference ± SEM (95% CI)** [estimated change in letters]	**p-value**
	Idebenone	**Placebo**		
ITT, n	53	29		
ITT, Week 24	-0.054 (-0.114, 0.005) [+ 2 letters]	0.046 (-0.032, 0.123) [-2 letters]	-0.100 (-0.188, -0.012) [5 letters]	0.026
Subgroup: Best eye LogMAR <1 at baseline, n	11	6		
Subgroup: Best eye LogMAR <1 at baseline, Week 24 (MMRM)	-0.3265	0.2552	-0.5817	0.1667
Subgroup: Best eye LogMAR >=1 at baseline, n	95	50		
Subgroup: Best eye LogMAR >=1 at baseline, Week 24 (MMRM)	-0.0617	0.0265	-0.0882	0.0330
Test for interaction (3-way)				0.7230

Abbreviations: CI – Confidence interval; logMAR - Logarithm of the minimal angle of resolution; MMRM – Mixed-model repeat measures; SEM – Standard error of mean; VA – Visual acuity

Table 21. Secondary outcome efficacy results (RHODOS) – Change in best visual acuity

	Estimated Change (95% CI) [estimated change in letters]		**Estimated Difference ± SEM (95% CI)** [estimated change in letters]	**p-value**
	Idebenone	**Placebo**		
ITT, n	53	29		
ITT, Week 24	-0.030 (-0.120, 0.060) [+1 letter]	0.098 (0.020, 0.215) [-4 letters]	-0.128 (-0.262, 0.006) [6 letters]	0.061
Subgroup: Best eye LogMAR <1 at baseline, n	8	4		

	Estimated Change (95% CI) [estimated change in letters]		Estimated Difference ± SEM (95% CI) [estimated change in letters]	p-value
	Idebenone	Placebo		
Subgroup: Best eye LogMAR <1 at baseline, Week 24 (MMRM)	-0.3093	0.7047	-1.014	0.0602
Subgroup: Best eye LogMAR >=1 at baseline, n	45	25		
Subgroup: Best eye LogMAR >=1 at baseline, Week 24 (MMRM)	-0.0456	0.0157	-0.0613	0.316
Test for interaction (3-way)				0.0332

Abbreviations: CI – Confidence interval; logMAR - Logarithm of the minimal angle of resolution; MMRM – Mixed-model repeat measures; SEM – Standard error of mean; VA – Visual acuity

Despite the small numbers, the analyses of the secondary outcomes suggest that idebenone could be more effective when treating patients that are not yet blind; this might be expected from an understanding of the disease process and the mode of action of idebenone.

B.2.8 Meta-analysis

A meta-analysis was not conducted, as the only relevant clinical trials identified were the RHODOS trial, RHODOS-OFU single-visit follow-up trial, and the LEROS trial.

B.2.9 Indirect and mixed treatment comparisons

As head-to-head comparison data from the RHODOS randomised clinical trial were available to inform the clinical efficacy of idebenone in LHON versus SoC, no indirect or mixed treatment comparison was undertaken.

B.2.10 Adverse reactions

B.2.10.1 Summary of studies that provide evidence of the adverse reactions

Safety data were available from the RHODOS trial, the single open-label follow-up visit (RHODOS-OFU) and EAP. In RHODOS, the incidence of all AEs and treatment related AEs were low and similar or lower with idebenone compared to placebo. No other relevant safety findings were derived from the RHODOS-OFU. In addition, data from the EAP suggests that idebenone was well-tolerated with a good safety profile and was in line with the results from the RHODOS trial.

B.2.10.2 RHODOS trial

All 85 patients in the safety population were evaluated for safety and tolerability. Compliance with study medication intake was high (mean pill count compliance of 96.5%, SD 6.8%). Overall, the incidence of all AEs and treatment related AEs were low and were either similar or lower with idebenone compared to placebo. The nature, severity and frequency of the AEs observed were indistinguishable between the study groups (12). The most common AEs (those with an occurrence of >5% in either group, regardless of causality) are collated in Table 22 below.

Table 22. Common adverse events reported by ≥5% of subjects in the RHODOS study

N (%) subjects	Idebenone 900 mg/day (N=55)	Placebo (N=30)	All Subjects (N=85)
Cardiac disorders			
Left ventricular hypertrophy	4 (7.3)	0	4 (4.7)
Gastrointestinal disorders			
Upper abdominal pain	3 (5.5)	3 (10.0)	6 (7.1)
Constipation	2 (3.6)	3 (10.0)	5 (5.9)
Diarrhoea	5 (9.1)	3 (10.0)	8 (9.4)
Flatulence	0	2 (6.7)	2 (2.4)
Vomiting	4 (7.3)	2 (6.7)	6 (7.1)
Infections and infestations			
Gastroenteritis	1 (1.8)	2 (6.7)	3 (3.5)
Influenza	6 (10.9)	3 (10.0)	9 (10.6)
Nasopharyngitis	14 (25.5)	5 (16.7)	19 (22.4)
Sinusitis	1 (1.8)	2 (6.7)	3 (3.5)
Investigations			
Alanine aminotransferase increased	1 (1.8)	3 (10.0)	4 (4.7)
Blood cholesterol increased	0	2 (6.7)	2 (2.4)
Blood creatine phosphokinase increased	1 (1.8)	2 (6.7)	3 (3.5)
Blood triglycerides increased	6 (10.9)	3 (10.0)	9 (10.6)
Gamma-glutamyl transferase increased	0	5 (16.7)	5 (5.9)
Musculoskeletal and connective tissue disorders			
Arthralgia	0	2 (6.7)	2 (2.4)
Back pain	4 (7.3)	2 (6.7)	6 (7.1)

N (%) subjects	Idebenone 900 mg/day (N=55)	Placebo (N=30)	All Subjects (N=85)
Nervous system disorders			
Dizziness	3 (5.5)	0	3 (3.5)
Headache	13 (23.6)	6 (20.0)	19 (22.4)
Respiratory, thoracic, and mediastinal disorders			
Cough	6 (10.9)	0	6 (7.1)
Oropharyngeal pain	5 (9.1)	3 (10.0)	8 (9.4)
Skin and subcutaneous tissue disorders			
Pruritus generalised	1 (1.8)	2 (6.7)	3 (3.5)
Rash	2 (3.6)	2 (6.7)	4 (4.7)

Source: European Medicines Agency. Raxone® (idebenone) European Public Assessment Report, 2015(12)

The majority of subjects had at least one AE (89% for idebenone, 87% for placebo) which were mild or moderate in intensity. The AEs reported by ≥10.0% of subjects on idebenone at the Medical Dictionary for Regulatory Activities preferred term (PT) level were: nasopharyngitis (25.5% of subjects affected), headache (23.6%), and influenza, blood triglycerides increased and cough (10.9% each). Headache, nasopharyngitis and cough were more frequent in the idebenone group than the placebo group. In addition, dizziness was reported at a higher incidence in subjects receiving idebenone (5.5%) compared to subjects receiving placebo (0%). One patient in the idebenone group discontinued treatment due to abnormal liver function test results that were possibly related to treatment. (12,17)

Two serious adverse events (SAEs) were reported: a case of infected epidermal cyst (idebenone group) and one case of epistaxis (placebo group). However, both were considered unrelated to the study medication. No clinically significant changes of vital signs and other biochemical or haematological parameters were observed.(12,17)

B.2.10.3 RHODOS-OFU

Of the 60 patients included in the safety population of RHODOS-OFU, there was one SAE of hypertensive emergency experienced on the day of the RHODOS-OFU visit, which was over 3 years after completing treatment with idebenone in RHODOS. The investigator considered this event not related to the idebenone received in the RHODOS trial. No other relevant safety findings were derived from the RHODOS-OFU.(8,12)

B.2.10.4 Expanded Access Programme

The safety profile of idebenone in this longer-term study is consistent with results from the RHODOS trial. In the 111 patients treated with idebenone, 65 AEs (60.7% mild; 4.5% moderate; 4.5% severe) were reported in 32 patients. The most common AEs were gastrointestinal (n = 17), with diarrhoea the most frequent (n = 5). Nine serious AEs were reported in seven patients (all considered “not related” to treatment). Three cases with fatal outcome, unrelated to idebenone use, were reported. Nine patients discontinued treatment due to AEs, due to the lack of efficacy, or occurrence of AEs, or a fatal outcome.(19)

B.2.11 Ongoing studies

One post-authorisation safety study with idebenone, the PAROS trial, is due to be published within the next 12 months (Q2 2024) (47). This is a prospective, non-interventional study of the clinical experience in patients with LHON treated with idebenone. The study results will focus on long-term safety of idebenone treatment and are unlikely to impact this assessment.

In addition to this, CaRS II, details of which can be found in Appendix M, is due to published in Q2 2024. This study is a retrospective, observational CaRS conducted to establish the clinical course (natural history) and VA outcomes in patients with LHON.

There are no other ongoing studies that will provide additional efficacy evidence in the next 12 months for idebenone in the indication being appraised in the submission.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Clinical effectiveness

The clinical study programme for idebenone in LHON represents a significant advancement in this rare disease area and demonstrates robust efficacy of idebenone in preventing vision loss due to LHON. RHODOS was the first double-blind placebo-controlled study in LHON and included patients with the full spectrum of LHON at baseline from early progressive to chronic stages where both eyes were “off-chart”. As no active comparator exists, the RHODOS study is relevant in comparing outcomes with idebenone and current SoC. The totality of the data presented provides strong evidence for a treatment benefit for idebenone in patients with LHON.

In the RHODOS trial, when administered for 6 months, a higher proportion of idebenone-treated LHON patients were prevented from VA loss (CRS) or presented with an improvement in VA (CRR) compared to placebo-treated controls. Although the primary endpoint was not met over the course of the 24-Week study, significant and medically relevant benefits of idebenone treatment were observed across the secondary endpoints and post-hoc analyses in the study population.(17)

This was validated by the EAP, where idebenone treatment led to improved outcomes by preventing VA loss and by promoting CRR, thereby reducing the number of patients with off-chart VA compared to the natural course of the disease. Results from this programme also suggested that the proportion of patients with CRR and the treatment effect size can be increased by treatment for 12 months or more.(19)

LEROS, a Phase 4 study designed to confirm the long-term efficacy of idebenone, confirmed that idebenone can prevent further vision loss and promote recovery of vision in patients. After 12 months of treatment, 43.1% of patients treated with idebenone achieved a CRB with high statistical significance, compared to eyes in the matching external natural history control group.(53) Further details on the long-term efficacy of idebenone is located in Appendix M.

There is no evidence of the loss of treatment benefit of idebenone following discontinuation of therapy.

B.2.12.2 Safety

The safety evidence demonstrates that in the placebo-controlled RHODOS trial, at a dose of 900 mg/day administered to LHON patients for 6 months, idebenone was safe and well-tolerated. The nature and frequency of AEs reported in patients receiving idebenone were similar to those observed with placebo. No potential safety signal emerged from the review of vital signs, laboratory and electrocardiography data. Idebenone was also well-tolerated over a duration of two years of treatment in the LEROS trial (see Appendix M1.1 LEROS trial), and no new safety concerns were observed further supporting the RHODOS study results. This was also supported by UK clinicians.(26) Combined with the generally well-tolerated safety profile for idebenone from extensive clinical use, the data presented provide evidence in support of a favourable benefit-risk assessment for idebenone in the treatment of the rare condition of LHON.

B.2.12.3 Strengths of the clinical evidence

Results from RHODOS, RHODOS-OFU, the EAP and LEROS demonstrate that there is a consistent clinical benefit of treatment with idebenone across multiple trials. The positive results from RHODOS have been validated through confirmatory studies (EAP and LEROS). The consistency of these results provides strength and validity to the findings of the primary and secondary endpoint analyses in RHODOS.

Clinical experts consulted by the Company also confirmed that the populations studied in the RHODOS, RHODOS-OFU, and LEROS trials were generalisable to LHON clinical practice in England. Additionally, the clinical experts agreed that the long-term disease progression trends observed in the RHODOS-OFU and LEROS trials were reflective of disease progression seen in clinical practice.

B.2.12.4 Limitations of the clinical evidence

The RHODOS trial was of relatively short duration (24 weeks), which may not have been long enough to fully assess the benefit of idebenone, as validated by clinical experts. However, to address this we have included the findings of the LEROS trial (see Appendix M1.1) which had a two-year duration and demonstrated the long-term treatment benefits with idebenone in LHON by showing that treatment over two years can prevent further deterioration of VA and recover lost VA in a significant and clinically relevant manner, independent of gender, age, mutation, severity of vision loss and time since symptom onset.(14) Additionally in the EAP, which supported regulatory approval and demonstrated the effect of idebenone over a longer time period (mean treatment duration of 25.6 months [2.4-70.4]), a longer treatment duration disclosed a higher rate of responding patients and a greater magnitude of improvement in recovery.(19) The limitations of the EAP were the retrospective nature of the data, lack of control group and the fact that EAP did not include chronic LHON patients. However, it provides an important view of long-term response and tolerability of idebenone in a real-world setting.(19)

B.2.12.5 Conclusion

Idebenone would present a step change in the management of LHON as the first and only licensed treatment for patients with LHON in England as current supportive treatments available for LHON patients do not prevent vision loss or allow recovery of VF.(11,12)

The clinical efficacy of idebenone in preventing vision loss and improving VA as well as the long-term safety data have been demonstrated in key clinical trials such as the RHODOS and RHODOS-OFU clinical studies, the EAP, and LEROS studies.(12,17–22,47) The studies present compelling evidence demonstrating the clinical benefits of idebenone and its substantial impact on patients with LHON.

The burden of LHON represents a severe unmet need, as the rapid vision loss associated with the disease causes patients to suffer from extreme disruption to all aspects of their lives, including education, career, recreation, and relationships, often exacerbated by the relatively young age of symptom onset.(7,54) This has a severe negative impact on patients' quality of life, as well as that of caregivers. Therefore, there is a substantial unmet need for new treatments such as idebenone to prevent vision loss in patients with LHON.

The clinical evidence from the RHODOS, RHODOS-OFU, LEROS and EAP studies demonstrates that idebenone is a generally well-tolerated and effective treatment for vision loss due to LHON. Idebenone has the potential to alleviate the severe burden of LHON on patients by preventing and recovering vision loss and improve the quality of life of patients and carers.

B.3 Cost-effectiveness

No published economic evaluations of idebenone were identified in the economic SLR. The economic model was therefore based on previous health technology assessment (HTA) appraisals for idebenone. (15,16,55)

The model structure is a multistate Markov model which has eight health states based on VA, as measured by the ETDRS logMAR chart. This is similar to previous HTA appraisals conducted in eye conditions.

The model adopted a lifetime time horizon and 3.5% discount rate, as per the NICE reference case (56). A cycle length of 3 months was used to align with the time points of data collection in the RHODOS and EAP studies. A mid-cycle correction is applied.

Given the available literature with suitable utility values conducted with patients with vision loss, Brown *et al.* was considered the most appropriate source to inform HRQoL in this cost-effectiveness analysis (CEA). Furthermore, Brown *et al.* has been used in the CEA of idebenone in previous HTA appraisals. (15,16,55)

Resource use was informed using a key opinion leader (KOL) survey (2022) conducted by Chiesi and subsequently validated by UK clinicians. (26,34) Costs were sourced from the National Schedule of Reference Costs and Meads *et al.* and inflated using the Unit Costs of Health and Social Care manual (2021), Personal Social Services Research Unit (PSSRU), if required.(57,58)

The CEA demonstrated that patients treated with idebenone accrued an additional [redacted] quality-adjusted life years (QALYs) compared to SoC, at an additional cost of £[redacted] per patient. Thus, corresponds to an incremental cost-effectiveness ratio (ICER) of £20,307 per QALY gained, with a PAS discount of [redacted]%.

Sensitivity analyses demonstrated that the economic results are robust to changes in key model outputs. Within the deterministic sensitivity analysis, the main drivers of the analysis are the total utility for the hand motion health state and the cost of supportive living. Within the scenario analysis, the largest deviations from the base-case ICER came from the discount rates for cost and outcomes set to 0% and 6%.

B.3.1 Published cost-effectiveness studies

An SLR was undertaken on February 25th 2022 with an update conducted on March 10th 2023 to identify published economic studies relevant to the decision problem. The methods, search strategies and inclusion and exclusion criteria used, along with results for the SLR of cost-effectiveness studies are provided in Appendix G.

Overall, six relevant cost-effectiveness publications were identified based on the selection criteria (Table 23). As part of the SLR, a total of 274 records were identified, of which 87 were excluded. Title/abstract screening was performed on 187 records, and 33 records were selected for further full-text review. No additional records were identified and included in full-text review from congress search and bibliographic search. Overall, six records (five original studies and one sub-analysis in the form of an abstract as an update to one of the original studies) were included for economic data extraction.

Of the five original studies, four were retrospective design with the data from chart review (one study), a cohort study, and a database review (two studies). One study was a cost-of-illness study. All studies were conducted in western countries, with two in North America (US/Canada), one in Finland, one in the United Kingdom, and one in Italy. No economic evaluation of interventions was identified.

Table 23. Summary list of published cost-effectiveness studies

Study	Cost year (currency)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
Gong *et al.* 2021(59) Daly *et al.* 2021 (abstract)(60)	2021	Cost-of-illness	Persons living with inherited retinal diseases, LHON inclusive	NR	US dollar; Canadian dollar US [US$ mil (%)] - Health system costs: 963.8 to 2,216.8 Canada [CAN$ mil (%)] - Health system costs: 37.8 to 144.3 US [US$ mil (%)] - Productivity costs: 1,854.9 to 4,409.3 - Caregiver costs: 1,077.0 to 2,560.1 - Deadweight loss: 706.0 to 1,662.9 - Loss of wellbeing: 8,431.7 to 20,043.6	NR
Lowry *et al.* 2020(61)	2020	Retrospective, Chart review	Patients seen in the Ocular Genetics Clinic (OGC) at the University of Arkansas for Medical Sciences (UAMS) Jones Eye Institute from 2009 to 2018	NR	NR	NR
Hahl *et al.* 2013(62)	2013	Retrospective, Database		NR	Euro Conditional Reimbursement decision concerning treatment for LHON fell	NR

Study	Cost year (currency)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
					within the cost range of €20,000 to €60,000	
Appleton *et al.* 2013(63)	2013	Retrospective, Database	Patients for genetic testing, LHON inclusive	NR	British pound Median cost per genetic diagnostic test: £225 (range: £95–950)	NR
Gorini *et al.* 2022(64)	2022	Retrospective, Cohort study	Patients with one of the conditions surveyed by the population-based Tuscany Registry of Rare Diseases and diagnosed between 2000-2018	NR	NR	NR

Abbreviations: ICER - Incremental cost-effectiveness ratio, LHON – Leber‘s hereditary optic neuropathy; QALYs – Quality-adjusted life years; US – United States

B.3.2 Economic analysis

No published economic evaluations of idebenone were identified in the economic SLR (Section B.3.1 and Appendix G). However, previous HTA appraisals have been conducted for idebenone within other HTA bodies (Scottish Medicines Consortium [SMC], All Wales Medicines Strategy Group [AWMSG], National Centre for Pharmacoeconomics [NCPE]).(15,16,55) Therefore, the economic model used within the previous idebenone appraisal was used and adapted accordingly to assess the cost-effectiveness of idebenone vs. SoC for patients with LHON in England.

Relevant HTAs (including previous NICE TAs) were identified in a targeted literature review and used to inform the de novo model structure, assumptions and data sources. These TAs included treatments recommended by NICE in other eye diseases (HST 11(65), TA298(66)) and idebenone appraisals with other HTA bodies (SMC, AWMSG and NCPE).(15,16,55)

B.3.2.1 Patient population

The patient population considered in the CEA is patients aged 12 years and older with LHON which is consistent with the licensed indication and the SmPC, the final NICE scope and the population from the clinical trials (RHODOS, EAP, LEROS), as detailed in Section B.2. (17,24,52)

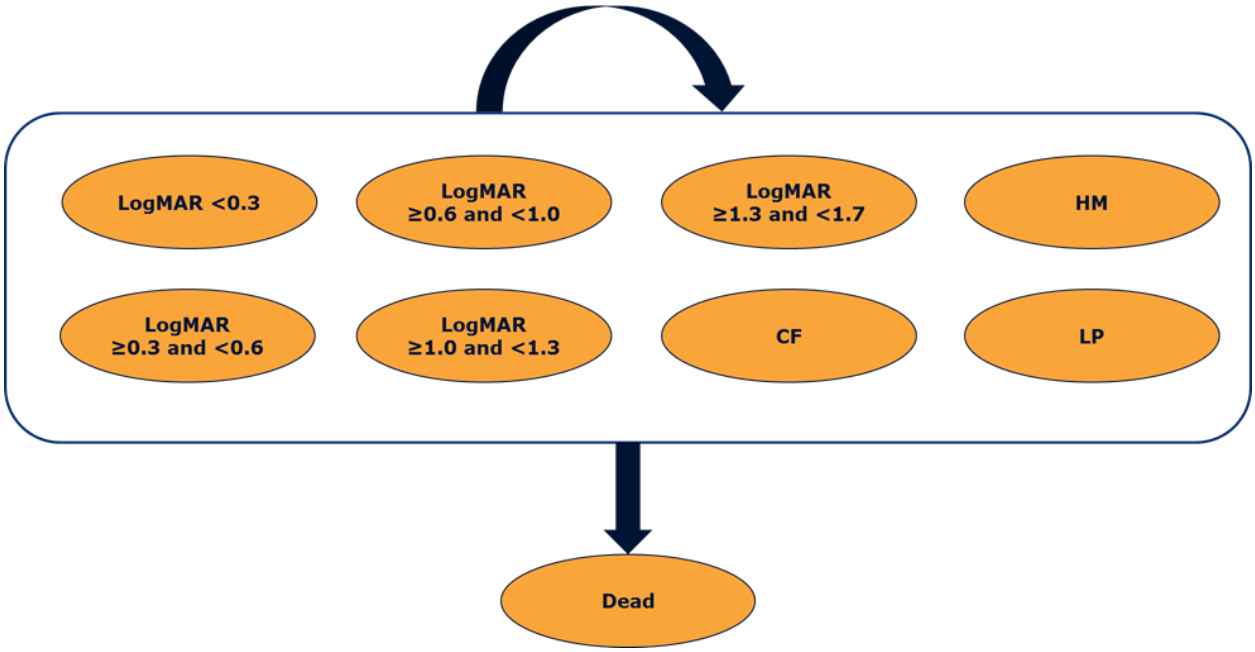
The baseline characteristics of the cohort entering the model are representative of the eligible patient population, as confirmed by UK clinicians.(26) Patients enter the model at age 34 years, in line with the mean age in the RHODOS clinical trial.(17)

B.3.2.2 Model structure

The model structure (Figure 1) is a multistate Markov model which has eight health states based on VA, as measured by the ETDRS logMAR chart. VA is quantified by logMAR score; for example “20/20” vision represents a logMAR score of 0, whilst legal blindness represents a logMAR ≥ 1. Please see Section B.1.1.1 for further details.

To capture the full cost and utility impact of preventing blindness, health states defined as logMAR just above and below 1 were also considered. However, since severity levels are variable within and outside legal blindness, additional logMAR health states were specified based on international guidelines describing the severity of visual impairment and published literature detailing the differences in quality of life by VA levels.(23,67) Finally, death was specified as an absorbing state in the model. The defined health states included in the model were validated by UK clinicians and all clinicians believed that the model structure fully captures the clinical and economic burden of LHON. (26)

Figure 20: Model Structure



Abbreviations: CF – Counting Fingers; HM – Hand Motion; LP – Light Perception
NB: CF, HM and LP correspond to logMAR 2.0, 2.3 and 2.6 in the RHODOS and EAP studies

Patients transition between all eight logMAR health states (logMAR<0.3; logMAR ≥0.3 and <0.6; logMAR ≥0.6 and <1.0; logMAR ≥1.0 and <1.3; logMAR ≥1.3 and <1.7; CF; Hand Motion [HM]; and Light Perception [LP]) and death as follows:

- Two cohorts, each with 1,000 patients, enter the model across the eight health states based on the baseline demographics of patients in the RHODOS study. One cohort receives idebenone whilst the other receives no treatment (SoC).
- For each cohort:
    - Patients that die transition to the death state.
    - Surviving patients transition between the logMAR health states based on treatment-specific transition matrices.
    - A mid-cycle correction is applied.
- For each cycle, total costs and QALYs are calculated based on the distribution of patients across the logMAR health states and death. These are accumulated over the model time horizon to calculate total costs and QALYs for the two cohorts from which incremental results and the cost per QALY are determined.

For the analysis, VA in the better-seeing eye is used for the baseline distribution and transitions of patients across logMAR VA states. As detailed in Section B.2.3, the change in best VA was the main secondary endpoint within RHODOS. It was considered to be the endpoint most relevant to clinical practice and the one that best reflects the impact of the disease on a patient, being the closest related to VF in daily life (12,17). This was further validated by UK clinicians (see Appendix N for further details). Furthermore, during protocol assistance the CHMP agreed with the rational for including this endpoint and also agreed that it may be more clinically relevant than the primary endpoint analysis which was the best recovery in VA.

Additionally, Brown *et al.* has demonstrated that a patient's quality of life is attributed more by the better-seeing eye than the worst-seeing eye.(23) This point from Brown *et al.* was also acknowledged by the External Assessment Group (EAG) in the assessment of the better-seeing eye model for aflibercept solution for injection for treating wet age-related macular degeneration (TA294).(68) For alignment, the utility values from Brown *et al.* (1999) have also been used in the base-case of this CEA. The better-seeing eye also has a higher predictability and consistency when measuring quality of life compared to the worst-seeing eye.

Furthermore, a better-seeing eye approach has also been used in previous NICE HTA appraisals (TA274, TA294, TA298). (66,68,69)

B.3.2.2.1 Rationale for model structure

A Markov model was considered the most appropriate model structure to assess the cost-effectiveness of idebenone for the following reasons:

Aligns with previous NICE and UK HTA submissions

A Markovian model approach has been used in previous NICE HTA submissions for eye conditions (Table 24), which were accepted by the Evidence Review Group (ERG) and committee (65,66):

- HST 11 (Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations): This CEA adopted a Markovian state-transition cohort structure which comprised of five "alive" health states, designed to capture the progressively severe levels of visual impairment, plus a sixth absorbing death health state. The "alive" health states were informed using American Medical Association (AMA) guidelines and defined as:
    - Moderate low vision (LogMAR better than 1.0)
    - Severe low vision (LogMAR between 1.0 – 1.4)
    - Profound low vision (LogMAR between 1.4 – 1.8)
    - Near-blindness (LogMAR worse than 1.8)

- Total blindness (no LP)

- TA274 (Ranibizumab for treating diabetic macular oedema): This CEA adopted a Markov model consisting of eight health states. The health states were defined by BCVA in the treated eye, rather than both eyes, and used 10-letter categories (with the exception of the best and worst states), resulting in eight health states excluding death:
  - 0-25 letters
  - 26-35 letters
  - 36-45 letters
  - 56-65 letters
  - 66-75 letters
  - 76-85 letters
  - 86-100 letters
- TA283 (Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion): This CEA adopted a Markov model which comprised of nine different health states; eight different intervals of BCVA and a ninth absorbing health state 'death'. Health states were defined as bands of 10 EDTRS letters (2 lines) in the better-seeing eye based on the assumption that 2-line changes are clinically significant with a provided Snellen equivalent:
  - 86-100 letters (Snellen equivalent: 20/16 – 20/10)
  - 76-85 letters (Snellen equivalent: 20/32 – 20/20)
  - 66-75 letters (Snellen equivalent: 20/64 – 20/40)
  - 56-65 letters (Snellen equivalent: 20/80 – 20/50)
  - 46-55 letters (Snellen equivalent: 20/125 – 20/80)
  - 36-45 letters (Snellen equivalent: 20/200 – 20/125)
  - 26-35 letters (Snellen equivalent: 20/320 – 20/200)
  - <25 letters (Snellen equivalent: <20/320)

- TA298 (Ranibizumab for treating choroidal neovascularisation associated with pathological myopia): This CEA adopted a Markov model which comprised of eight states, defined by a 10-letter range in BCVA in the treated eye, and one absorbing death health state. The eight health states correspond to levels of BCVA defined according to the ETDRS letters scale with approximate equivalent Snellen values provided:
    - 86-100 letters (Snellen equivalent: 20/16 – 20/10)
    - 76-85 letters (Snellen equivalent: 20/32 – 20/20)
    - 66-75 letters (Snellen equivalent: 20/64 – 20/40)
    - 56-65 letters (Snellen equivalent: 20/80 – 20/50)
    - 46-55 letters (Snellen equivalent: 20/125 – 20/80)
    - 36-45 letters (Snellen equivalent: 20/200 – 20/125)
    - 26-35 letters (Snellen equivalent: 20/320 – 20/200)
    - <25 letters (Snellen equivalent: <20/320)

The modelling approach in previous TAs follow a similar structure to this idebenone appraisal (Figure 20). The health states defined in the model structure for TA283 and TA298 adopted the ETDRS letter scale, a form of logMAR chart, which is the same scale of measure used in the model structure for this CEA.

Additionally, the model structure detailed in Section B.3.2.2 for assessing the cost-effectiveness of idebenone for patients aged 12 years and older with LHON has already been assessed and accepted by other UK HTA bodies, including SMC, AWMSG and NCPE. (15,16,55)

Uses health states that align with the outcomes in the clinical trials

The measure of logMAR health states, as defined by the ETDRS scale, also aligns with the outcomes measured in the clinical trials for idebenone.

As detailed in B.2.3, the primary efficacy endpoint of the RHODOS study was the ‘best recovery of logMAR VA between baseline and Week 24 in either right or left eye’ and the main secondary efficacy endpoint was the ‘change in best VA at Week 24 (best eye at Week 24) compared to best VA at baseline’. The EAP study measured the CRR in VA from nadir which is measured by the improvement from an off-chart best VA to on-chart by the equivalent of at least one full line on an ETDRS chart or an improvement in an on-chart best VA by the equivalent of at least two lines (10 letters).

Is considered more appropriate than a patient-level simulation model

A patient-level simulation structure was considered as a potential option for this CEA as the approach provides the ability to model vision in both eyes (70). However, as previously stated, the better-seeing eye is considered the most important for measuring VA (Section B.3.2.2). (23) Furthermore, a patient-level simulation approach is data intensive and has a high computational burden which is not optimal or feasible for modelling LHON given the limited data available. Attempting to use a patient-level simulation with limited data will only add to the uncertainties and limitations raised in the CEA.

Therefore, given the above, the Markov model structure aligns well with important aspects of the disease, previous NICE HTAs and previous UK HTAs for idebenone and is considered the most appropriate structure for this CEA.

B.3.2.2.2 Time horizon and cycle length

The base-case CEA adopts a 'lifetime' horizon of 66 years, which is considered long enough to adequately capture the lifetime of patients in this setting (the mean starting age in the CEA is 34 years, which is aligned with the baseline characteristics in RHODOS).(17)

A cycle length of three months is selected based on the time points of data collections in the RHODOS and EAP studies. A mid-cycle correction was applied assuming patients entered/exited health states half-way through a cycle.

B.3.2.2.3 Discount rate and perspective

As per the NICE reference case, the analysis is conducted from the perspective of the NHS and Personal Social Services (PSS) for costs and health outcomes.(56) All health outcomes are measured in QALYs, and a 3.5% discount rate per annum is used for QALYs and costs. (56)

Features of the economic analysis

Table 24 presents the key features of the economic analysis in comparison to previous NICE appraisals of other technology appraisals for similar eye diseases. These include:

- HST 11: Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations (65)
- TA274: Ranibizumab for treating diabetic macular oedema (69)
- TA283: Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion (71)
- TA294: Aflibercept solution for injection for treating wet age-related macular degeneration (68)
- TA298: Ranibizumab for treating choroidal neovascularisation associated with pathological myopia (66)

Table 24. Features of the economic analysis

	Previous appraisals					Current appraisal	
Factor	**HST11**(65)	**TA274** (69)	**TA283**(71)	**TA294**(68)	**TA298**(66)	**Chosen values**	**Justification**
Model type	Markovian state-transition cohort model with health states based on average vision on VA and VF	Markov model with eight health states defined by BCVA in the treated eye.	Markov state-transition model with eight BCVA health states.	Markov state-transition cohort model with 30 health states defined by a combination of different levels of VA in both eyes	Markov model with health states defined by the BCVA in the treated eye and an absorbing death state.	Markov model with eight health states defined by BCVA and one absorbing 'death' health state.	A Markov model approach aligns with previous NICE HTA examples, previous idebenone appraisals, clinical expert input and makes best use of the available data.
Perspective	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	As per NICE reference case (56)
Time horizon	Lifetime horizon	15 years	15 years	Lifetime horizon	Lifetime horizon	Lifetime horizon	As per NICE reference case (56)
Cycle length	One year	3 months	1 month	1 month	3 months	3 months	Considered sufficient to capture the clinical outcomes reported by patients with LHON in the clinical studies
Discount rate	3.5%	N/A	N/A	3.5%	3.5%	3.5%	As per NICE reference case (56)
Outcome measure	QALYs	QALYs	QALYs	QALYs	QALYs	QALYs	As per NICE reference case (56)
Source of utilities	**Patients:** Company - derived via expert elicitation	EQ-5D data from RESTORE. Scenario analysis included Lloyd	Company – Brown *et al.* (1999) and later revised to Czoski-	EQ-5D data from VIEW 2. The ERG later suggested that Brown *et al.* be used for the	Czoski-Murray *et al.* 2009	Brown *et al.* (1999)	Given the available literature with suitable utility values conducted with patient of vision loss, Brown *et al.* was considered the most

	exercise (Lloyd *et al.* 2019) EAG preferred – Rentz *et al.* (2014) Scenario analysis - Brown *et al.*(1999) **Caregivers:** disutility (0.08) applied from Wittenberg *et al.* 2013 to HS2-5 for <18, half 18+	*et al.* and Czoski-Murray *et al.* (2009)	Murray *et al.* (2009)	better-seeing eye model.			appropriate alternative to inform HRQoL in this CEA. Furthermore, Brown *et al.* has been used in the CEA of idebenone for various other HTA appraisals. (15,16,55)
Source of costs	NHS cost collection BNF PSSRU	Cost data largely derived from the published costing study of blindness in the UK (Meads *et al.* [2003]).(58)	N/A	Resource use and unit costs associated with treatment and monitoring visits were based on Hospital Episode Statistics (HES 2010/11) and NHS cost collection (2011/12).7 Costs associated with blindness taken from a published costing study of	NHS cost collection PSSRU	NHS cost collection PSSRU	As per NICE reference case (56)

				blindness (Meads *et al.* [2003]).(58)			

Abbreviations: BCVA – Best-corrected visual acuity; NHS – National Health Service; NICE – National Institute of Health and Care Excellence; PSS – Personal Social Services; QALYs – Quality-adjusted life years; VA – Visual acuity; VF – Visual field; VN – Voretigene neparvovec

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention: idebenone

Idebenone is an oral therapy. Each film-coated tablet contains 150 mg idebenone. The dose used in the CEA is 900 mg/day idebenone (two tablets, three times a day) which aligns with the SmPC and licensed therapeutic dose. (24)

B.3.2.3.2 Comparators: standard of care

Other than idebenone, no other licensed therapeutic options exist for patients with LHON in England and idebenone would be expected to be used as a first-line therapy.

Therefore, SoC for LHON in England is the only comparator in this CEA and consists of established clinical management, which includes visual aids, occupational and low vision rehabilitation and lifestyle management (no smoking, reduced alcohol consumption, diet that includes fresh fruit and vegetables). This definition of SoC aligns with the final scope for idebenone and has been validated by UK clinicians.(26)

In the CEA, SoC is captured within the model through resource use associated with each health state. Therefore, in the comparator arm SoC costs are accumulated through the time spent in the various health states. As resource use costs are also accumulated in the idebenone arm, the CEA assumes that patients receiving idebenone also receive SoC. This approach has been demonstrated in various other NICE HTAs, including HST11.(65)

B.3.3 Clinical parameters and variables

B.3.3.1 Baseline characteristics

The baseline characteristics used to inform the CEA are presented in Table 25 and are based on the RHODOS study as it is the key source of data and considered generalisable to the UK population, as confirmed by UK clinicians. (26) A more detailed summary of baseline patient demographics across clinical studies is provided in Section B.2.3.2.

Table 25: Baseline patient characteristics informing the economic model

Characteristic	Value	Source	Use in model
Mean age, years	34 years	RHODOS	Used to inform the estimation of background mortality.
Proportion female, %	14%		

B.3.3.2 Treatment effectiveness

As RHODOS is a randomised, double-blind, placebo-controlled, multicentre trial and the first to assess the clinical effectiveness of idebenone for the treatment of LHON, the data collected within this study was considered as the basis of this CEA. Furthermore, the NICE manual (2022) states that there is a strong preference for high-quality randomised controlled trial (RCT)s for the assessment of relative treatment effects.(56) However, as the 24-week duration of RHODOS was not long enough to demonstrate the full benefit that idebenone has on patients with LHON, further data was needed to supplement the clinical effectiveness of idebenone in the long-term.

Section B.2 and Appendix M detail the LEROS study, an external natural history controlled, open-label intervention study which assessed the efficacy and safety of long-term treatment with idebenone. LEROS was designed as a confirmative trial with evidence used to support the clinical effectiveness demonstrated in RHODOS. Section B.2 also details the EAP study, a RWE open-label, retrospective analysis identified in the SLR which assessed the long-term treatment with idebenone in patients with LHON.

However, whilst the RHODOS trial only consisted of idebenone-treated patients who carried the three mutations of LHON (G11778A [67.3%], T14484C [20%], G3460A [12.7%]), the ITT population within LEROS consisted of patients from a wider range of LHON mutations (G11778A [[redacted]%], T14484C [[redacted]%], G3460A [[redacted]%], Negative [[redacted]%], Other [[redacted]%]). UK clinicians noted that the G11778A mutation may be under-represented in the LEROS trial population. Whereas the EAP study, has a much more similar mutation distribution to RHODOS compared to LEROS; (G11778A [62.1%], T14484C [18.4%], G3460A [19.5%]). Furthermore, input from clinical experts suggests that different mutations may have a different impact on outcomes stating that patients with the T14484C mutation show a higher rate of spontaneous recovery.(26)

Furthermore, the LEROS trial had a [redacted]proportion of male patients within the ITT population ([redacted]%) compared to RHODOS (85.9%) and given that ~80-90% of LHON cases typically occurs in males, this may be an under-representation of the patient population seen in clinical practice.(29) However, the EAP study demonstrates a proportion of males included in the study closer to the proportion seen in the RHODOS study and clinical practice; 82%.

Therefore, it was considered appropriate to exclude LEROS data from the economic model due to the heterogeneity between the patient populations and generalisability to patients in UK clinical practice. Instead, we have used RWE in the form of the EAP study to supplement the data from RHODOS and inform the transition counts of the idebenone arm in the long-term. This also allows for longer follow-up of data to be incorporated into the CEA as the duration of the EAP study is 36 months compared to the 24-month duration of LEROS. The Company considers that this longer term data reduces the uncertainty in a rare disease where available data is already limited. This aligns with UK clinicians who confirmed that VA would be expected to remain stable after 3 years of treatment.(26) Furthermore, data from EAP has been used to support the long-term economic modelling of idebenone in other UK HTA submissions including SMC, AWMSG and NCPE. (15,16,55)

To further support the use of the EAP data, in the recently published NICE RWE framework, it is stated that the RWE could be used more routinely to fill evidence gaps and speed up access for patients where RCTs and non-randomised studies cannot. The updated NICE strategy 2021 to 2026 also aims to use real-world data to resolve gaps in knowledge and drive forward innovation.(72)

The following data sources (as described in Section B.2) were evaluated to inform the transitions between the logMAR health states:

- The RHODOS study [N=85 safety population; N=82 efficacy population]: enrolled patients that had experienced vision loss due to LHON within 5 years (mean time since onset of symptoms was 22.8-months). LogMAR was collected for idebenone and placebo patients at baseline, 3-months and 6-months. (17)

- The EAP study [N=87 efficacy population who all had one of the three common mutations and were within one year of onset of symptoms]: collected logMAR VA data for idebenone patients at baseline and every three months thereafter. Standardised follow-up is available for up to three years. (52)

- The CaRS studies [N=74 Natural history outcomes population not treated with idebenone (which forms the efficacy population of this analyses) and N=188 with previous idebenone use]: collected historically documented VA data from existing medical records in 11 participating clinical centres (10 Europe, 1 US). No inclusion criteria were specified, and data were collected non-systematically, without pre-selection, based on participating clinical centres record-keeping practices. (20) Despite not being identified in the SLR, the results of the CaRS study are included in the economic modelling in the SoC arm as they demonstrate the disease course of LHON in patients who only received SoC.

B.3.3.2.1 Idebenone transition probabilities

The clinical effectiveness of idebenone is captured by transitions between logMAR VA health states. The RHODOS study is the only RCT to compare idebenone with placebo. The placebo arm of the RCT is used to inform the SoC arm of this CEA. However, transitions between logMAR VA health states can only be derived from RHODOS up to six months and this is insufficient to determine how logMAR VA changes for idebenone patients over a long-term time horizon.

The EAP shows that when patients are treated with idebenone for over 6 months the response rates with regards to CRR improve; for patients with CRR from nadir, 45% (18/40), 67.5% (27/40), and 92.5% (37/40) had responded by 6, 12, and 24 months of treatment, respectively. The other patients (3/40) had their initial observation of CRR by 36 months of treatment. (19) The suitability of using the EAP data to determine how idebenone patients from the RHODOS study may transition between logMAR VA health states after six months was evaluated. Table 7 and Table 9 in Section B.2 demonstrates that baseline characteristics of idebenone-treated patients in the EAP and RHODOS studies were broadly similar in terms of age, gender, VA severity and mutation type but patients in the EAP study had a shorter time since onset compared to idebenone-treated patients in the RHODOS study. The method of analysis of logMAR VA was identical between the EAP and RHODOS studies, and studies collected data at three-monthly intervals. Finally, outcomes between the studies were broadly similar at six months; the proportion of patients with a CRR was 30.2% (16/53) for idebenone-treated patients in the RHODOS study compared to 46.0% (40/87) in the EAP study. (19,73)

Hence, the RHODOS and EAP studies were considered sufficiently similar in terms of population, analysis methods and outcomes to support the use of EAP to determine idebenone transition probabilities after six months. On the other hand, CaRS data were not used to inform idebenone transitions because the CaRS study did not provide sufficient information to determine when, for how long, and at what dose of idebenone had been used.

Therefore, transitions between logMAR VA health states for idebenone are determined by three-monthly transition matrices based on data from the RHODOS and EAP studies. Specifically, data from the RHODOS study informs transitions 0 to 3 months and 3 to 6 months, whilst EAP data from patients in the efficacy population (N=87), informs transitions 6 to 9 months up to 33 to 36 months, to align with the length of the EAP study. Although some patients in the EAP study did provide follow-up visits post 36 months, they occurred at variable time points and therefore could not be used to inform transitions post 36 months. As such, it was conservatively assumed the logMAR VA of patients remains unchanged after 36 months. UK clinicians confirmed that VA would be expected to remain stable after 3 years of treatment.

Due to the small patient numbers of the clinical studies, there are some instances where no data was collected to inform a transition from one health state to the seven alternative health states. Where this is the case, it was assumed that the patient remained in the same health state. This was considered the most reasonable alternative in the absence of the data and is a limitation due to the ultra-rare nature of LHON and limited patient numbers in the clinical studies.

Full transition probabilities are presented in Table 1 of Appendix J.

The probability of transitioning to death for patients in the idebenone arm is based on all-cause mortality rates stratified by age and gender from the general population of England in 2018 to 2020.(74) Evidence exists demonstrating that the risk of mortality is higher in patients with blindness and visual impairment. Since idebenone can prevent blindness and reduces visual impairment, it can be expected that treatment with idebenone would be associated with a reduced mortality risk compared to no treatment. However, given the lack of specific mortality data for idebenone, the conservative assumption is made that there is no treatment effect on mortality associated with idebenone. (75,76)

B.3.3.2.2 SoC transition probabilities

The clinical effectiveness of SoC is captured by transitions between logMAR VA health states in an untreated population. The RHODOS study informs transitions from baseline to six months, in line with the trial design and duration. However, beyond six months, RHODOS is insufficient to determine how logMAR VA changes for SoC patients over a long-term time horizon.

The suitability of using the CaRS data to determine how placebo patients from the RHODOS study may transition between logMAR VA health states after six months was evaluated. Table 7 in Section B.2.3 and Table 14 in Appendix M demonstrates that baseline characteristics of placebo-treated patients in the CaRS and RHODOS studies were similar in terms of age, gender and mutation type. The method of analysis of logMAR VA was identical between the CaRS and RHODOS studies, however data collected in the CaRS study had variable follow-up times.

To overcome this limitation, a windowing approach was used to classify CaRS patients into three-monthly visits. Patients with a visit ≥ 1.5 months and < 4.5 months were assigned the 3-month window, whilst patients with a visit ≥ 4.5 months and < 7.5 months were assigned to the 6-month window and so on. When considering this windowing approach, outcomes between the studies were similar at six months, despite the CaRS population having milder and earlier disease compared to RHODOS. The proportion of patients with a CRR from baseline to six months was 10.3% (3/29) for placebo-treated patients in the RHODOS study compared to 8.1% (6/74) in the CaRS study. This is likely due to the rapid onset of symptoms suggesting that disease course has significantly progressed by six months regardless of baseline VA. Hence, despite some heterogeneity in terms of the population and analysis methods, the similarity in outcomes confirmed the suitability of using CaRS data for determining transitions post six months. In addition, given the limited availability of data in patients treated with SoC, the only alternative option would be to only use RHODOS data up to 6 months and assume no change in VA after six months, which would be highly unrealistic given that there is still potential for further deterioration or spontaneous recovery post six months. Furthermore, a last observation carried forward (LOCF) approach was conservatively applied to impute missing data in the SoC arm. Without the LOCF approach, the patient numbers in the SoC arm remained small across the 36 months of transition probabilities and resulted in a considerably uncertain and low CEA ICER. EAP data were not used to inform no treatment transitions because the EAP study did not provide information for no treatment.

Therefore, transitions between logMAR VA health states for SoC are determined by three-monthly transition matrices based on data from the RHODOS and CaRS studies (Table 2, Appendix J). Specifically, data from the RHODOS study informs transitions 0 to 3 months and 3 to 6 months, whilst CaRS data informs transitions 6 to 9 months up to 33 to 36 months. Limited data is available from the CaRS study past 36 months, and it does not suggest visual acuity changes to a significant extent, therefore it is assumed that the logMAR VA of patients remains unchanged after 36 months.

As per the idebenone treatment arm, there are some instances where no data was collected to inform a transition from one health state to the seven alternative health states. Where this is the case, it was assumed that the patient remained in the same health state.

Full transition probabilities are presented in Table 2 of Appendix J.

The probability of transitioning to death for patients in the SoC arm is based on all-cause mortality rates stratified by age and gender from the general population of England in 2018 to 2020.(74) As detailed above, evidence exists demonstrating that the risk of mortality is higher in patients with blindness and visual impairment. (75,76) However, to align with the conservative assumption that there is no treatment effect on mortality associated with idebenone, it is also conservatively assumed that there is no effect on mortality associated with SoC.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality of life data from clinical trials

The RHODOS study collected HRQoL data in terms of change in Visual Function Index (VF-14), CGIC and energy levels using the VAS. However, no mapping algorithms are available to translate these condition-specific measures into utilities. Therefore, the HRQoL data collected from the RHODOS study could not be applied within the CEA.

B.3.4.2 Mapping of VF-14 to EQ-5D-3L

As stated in Section B.3.4.1, mapping of utility values in terms of VF-14 from RHODOS was not possible and therefore no mapping has been conducted.

B.3.4.3 Health-related quality of life studies

An SLR was undertaken on February 25th 2022, with an update carried out on March 10th 2023, to identify previous HRQoL data and studies relevant to the decision problem. The methods, search strategies and inclusion and exclusion criteria used, along with results for the SLR of HRQoL studies are presented in Appendix H.

A total of 623 records were identified through the initial Ovid platform search in all databases, with 216 records being excluded. Title/abstract screening was performed on the remaining 407 records, and 84 records were selected for further full-text review (323 excluded). A further 78 records were excluded; seven studies were excluded due to population, 21 studies were excluded due to intervention, 36 studies were excluded due to outcomes, 12 studies were excluded due to the study design and two studies were duplicates. Four additional abstracts were included in full-text review from the congress search and no records were identified from bibliographic search. Overall, 10 records (seven original studies and three updates) were included for HRQoL data extraction.

All seven original studies, consisting of RCTs (5 studies) (77–81), cross-sectional study (one study) (82), and qualitative interview (one study)(83) were conducted between 2019 and 2023. Five studies were conducted internationally, one was conducted in the US only, and the geographic setting of one study was not reported. A summary of studies extracted are presented in Appendix H, Table 53.

The National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) was the validated QoL scale used in all 5 RCTs. The VFQ-25 scale was reported as sub-scales in the following domains:

- Composite score
- General vision

- Ocular pain
- Near activities
- Distance activities
- Social functioning
- Mental health
- Role difficulties
- Dependency
- Colour vision
- Peripheral vision

Four of the five RCTs examined rAAV2/2-ND4 (GS010) gene therapy effects on QoL (77–79,81), the remaining RCT study examined the effects of elamipretide 1% , the qualitative interview study examined the effects of idebenone (83), and the cross-sectional study had no interventions specified (82). The four gene therapy RCTs (REVERSE, RESCUE, RESTORE, and REFLECT) reported mean VFQ-25 scores at baseline, and mean changes in VFQ-25 at end of follow-up, for the HRQoL evaluable populations. Across all gene therapy studies, data indicated that treatment could provide meaningful benefits in QoL, especially in general vision, mental health, role difficulties and dependency domains. There was also clinically significant improvement for the REVERSE participants in the general vision, colour vision, periphery vision, distance activities, and near activities. In contrast, RESCUE participants reported no significant improvements within those domains at measurement timepoint, and in fact reported clinically significant worsening for colour vision and peripheral vision.

Across all seven original studies and the three updated studies, none reported utility values and therefore could not be utilised in the CEA.

B.3.4.3.1 Targeted literature review

To overcome the lack of utility values found in the SLR, a targeted literature review of HRQoL in ophthalmological conditions (including LHON) was therefore conducted to identify any further studies or studies that may have been published after the SLR search date (March 10th 2023). Several studies were found that could be used to inform the utility values in the model and are detailed in the following sections.

B.3.4.3.1.1 Brown *et al.* 1999

Brown *et al.* 1999 was a study identified within the targeted literature review and provided utility values for all health states specified in the model structure (Section B.3.2.2). (23) This study collected time-trade off (TTO) utility values in the better-seeing eye for 325 patients with visual impairment of 20/40 or worse in one eye across a range of on-chart (up to logMAR 1.3) and off-chart (HM, CF, LP) visual acuities. Values were elicited using the TTO method using a VF-14 questionnaire for each health state. This was deemed a suitable alternative to EQ-5D as studies have shown that EQ-5D shows poor performance in detecting vision impairment. (84,85)

As the logMAR health states were based on a range as opposed to a point estimate, the mid-points for each range were used together with the Brown *et al.* published utilities to determine the most appropriate utility for each health state. For example, the mid-point between logMAR 0.3-0.6 is logMAR 0.45; the closest utility to this logMAR in the Brown *et al.* study was 0.77 (logMAR 0.4). Utility values derived from Brown *et al.* 1999 are presented in Table 26.

Table 26. Utilities by logMAR health state derived from Brown *et al.* 1999

Brown *et al.* visual acuity	Brown *et al.* utility (95% CI)	Mid-point health state	Model utility value
LogMAR = 0	0.92 (0.87-0.97)	LogMAR <0.3	0.84
LogMAR = 0.1	0.87 (0.82-0.92)		
LogMAR = 0.2	0.84 (0.79-0.89)		
LogMAR = 0.3	0.80 (0.74-0.86)	LogMAR 0.3-0.6	0.77
LogMAR = 0.4	0.77 (0.70-0.84)		
LogMAR = 0.6	0.74 (0.67-0.81)	LogMAR 0.6-1.0	0.67
LogMAR = 0.7	0.67 (0.57-0.77)		
LogMAR = 1.0	0.66 (0.55-0.77)	LogMAR 1.0-1.3	0.63
LogMAR = 1.2	0.63 (0.54-0.72)		
LogMAR = 1.3	0.54 (0.43-0.65)	LogMAR 1.3-1.7	0.54
CF	0.52 (0.36-0.68)	CF	0.52
HM-NLP	0.35 (0.10-0.60)	HM/LP	0.35

Abbreviations: CI – Confidence interval; CF – Counting fingers; HM – Hand motion; LP – Light perception; NLP – No light perception

B.3.4.3.1.2 Lawrence *et al.* 2023a

A recent study by Lawrence *et al.* 2023 provided utility values by health state for patients with LHON.(86) The first study by Lawrence *et al.* 2023a developed eight health state vignettes aligned with the health states specified in the model structure (Section B.3.2.2). A targeted literature review was conducted to characterise patient experience of LHON and published health state vignettes describing another rare inherited eye condition, RPE65-medaited inherited retinal disease, were used to develop the vignettes. Draft health state vignettes were developed based on the literature review and clinical trial data from the REFLECT study for lenadogene nolparvovec. Qualitative interviews were conducted with patients with LHON (N=9) and clinical experts (N=5) in the UK and Republic of Ireland (ROI) to validate the draft vignettes and the vignettes were revised following feedback.

B.3.4.3.1.3 Lawrence *et al.* 2023b

A follow-up study by Lawrence *et al.* 2023b then used the eight health state vignettes to elicit utility values.(87) Participants from the UK (N=301) and ROI (N=61) general public were recruited via an online recruitment platform and completed an online survey in which they were asked to rate four randomised health state vignettes using the Health State Utilities Indeix-3 (HUI-3) and EQ-5D-5L. A sub-sample, consisting of N=100 and N=20 participants from the UK and ROI, respectively, also competed a one on one TTO interview to assess all eight vignettes (including VAS). Utility values derived from Lawrence *et al.* 2023b for the UK population are presented in Table 27.

Table 27. Utilities by logMAR health state derived from Lawrence *et al.* 2023b for the UK population

Health state	HUI-3 (N=301)	EQ-5D-5L (N=297)	TTO (N=100)
LogMAR <0.3	0.838	0.786	0.874
LogMAR 0.3-0.6	0.504	0.625	0.746
LogMAR 0.6-1.0	0.436	0.583	0.686
LogMAR 1.0-1.3	0.351	0.506	0.546
LogMAR 1.3-1.7	0.314	0.498	0.496
CF	0.212	0.373	0.391
HM	0.183	0.343	0.404
LP	0.177	0.339	0.342

Abbreviations: CF – Counting fingers; HM – Hand motion; HUI-3 – Health Utilities Index-3; LP – Light perception; TTO – Time-trade off

B.3.4.3.1.4 Utilities used in previous NICE appraisals

As well as consideration for the utilities reported in literature, utilities reported in previous NICE appraisals that include patients with relevant eye conditions were also assessed for appropriateness of inclusion within the CEA.

Csozki-Murray *et al.* 2009

TA298 sourced utility values from Czoski-Murray *et al.* 2009. (66,88) Czoski-Murray *et al.* 2009 reports on a study that used contact lenses to simulate the effects of a visual impairment caused by age-related macular degeneration (ARMD). Utility values were elicited for three visual states representing different severities of ARMD from 108 healthy patients. Mean-adjusted TTO values were estimated for each lens grouped by four health state severity levels defined using distant VA (better-seeing eye) on the LogMAR scale. Table 28 presents the utility values derived from Czoski-Murrary *et al.* and used in TA298.

Table 28. Utilities by logMAR health state derived from Czoski-Murray *et al.* as used in TA298

Health state	Utility values
LogMAR <0.3	0.706
LogMAR 0.3-0.6	0.681
LogMAR 0.6-1.0	0.511
LogMAR 1.0-1.3	0.511
LogMAR 1.3-1.7	0.314
CF	0.314
HM	0.314
LP	0.314

Abbreviations: CF – Counting fingers; HM – Hand motion; LP – Light perception

Rentz *et al.* 2014

Within the HST 11 appraisal, the EAG preferred the use of a TTO study by Rentz *et al.* (2014)(89) to inform the utility values in their base-case. The study aimed to develop an algorithm to estimate health preference scores using health states generated from the Visual Function Questionnaire-Utility Index. The study consisted of 607 members of the general public (Australia, Canada, the UK and US) who were asked to perform TTO for eight health states with varying degrees of vision problems. The best health state was equivalent to no difficulty (health state 111111) and the worst health state was equivalent to substantial vision difficulties (including stopping of work and hobbies that require to see up close, limitations in how long a person can work and staying home all the time because of vision).

The Rentz *et al.* (2014) study derived utility values for a UK population (n=152). The eight health states are assumed to align with the eight health states used within this appraisal and are presented in Table 29.

Table 29. Utilities by logMAR health state derived from Rentz *et al.* as used by the EAG in HST 11

Health state	Utility values
LogMAR <0.3	0.916
LogMAR 0.3-0.6	0.851
LogMAR 0.6-1.0	0.795
LogMAR 1.0-1.3	0.717
LogMAR 1.3-1.7	0.687
CF	0.534
HM	0.378
LP	0.264

Abbreviations: CF – Counting fingers; HM – Hand motion; LP – Light perception

B.3.4.4 Adverse reactions

Full details regarding adverse event data in trials for idebenone can be found in Section B.2.10.

Most AEs observed in RHODOS were considered mild to moderate in intensity. Two SAEs were reported: a case of infected epidermal cyst (idebenone group) and once case of epistaxis (placebo group). However, both were considered unrelated to study treatment. There was one SAE of hypertensive emergency experienced on the day of the RHODOS-OFU visit, which was three years after completing treatment with idebenone. However, again, this was considered unrelated to study treatment.

In in the EAP study, nine SAEs were reported in seven patients, however, they were considered not related to treatment.

Given the above, and the full details in Section B.2.10, AEs were not included in the base- case CEA. Therefore, AE-related disutilities were not included in the base-case CEA. Furthermore, UK clinicians confirmed that any AEs observed in the RHODOS trial do not require hospitalisation or specialist treatment and that the safety profile of idebenone is very good.

B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

B.3.4.5.1 Patient HRQoL

For the CEA base-case, patient utility values derived from Brown *et al.* (1999) have been used to inform HRQoL of patients with LHON and are presented in Table 30.(23) Utility values derived from Brown *et al.* (1999) were considered the most appropriate to inform the base-case for the following reasons:

- The utility values have been used and accepted within numerous other HTA appraisals for idebenone.(15,16,55)

- Brown *et al.* (1999) has also been included in the assessment of various other NICE HTAs for eye conditions, including HST 11, TA283 and TA294. (65,68,71)

- The study derives utility values based on the better-seeing eye which aligns with the model structure of this CEA and transition of patients across health states. This has also been demonstrated in previous NICE TAs; in TA294 the ERG suggested that utility values for a better-seeing eye model should be taken from the study by Brown *et al.* (1999).(68)

- The study was conducted with a large sample size of 325 patients in a population generalisable to the UK population.

- Unlike the studies by Lawrence *et al.* and Rentz *et al.* (2014), all 325 patients completing the questionnaire had experienced varying levels of vision loss, predominantly with vitreoretinal diseases.

- UK clinicians also considered Brown *et al.* (1999) an appropriate source to use to inform utility values.(26)

The utility values presented in Rentz *et al.* were also considered an appropriate alternative to inform the base-case CEA as this source has been deemed suitable by previous EAGs (HST 11) and the utility values are presented within a UK population.(65,89)

The Company acknowledge that the study by Lawrence *et al.* (2023) presents utility values based on an EQ-5D-5L evaluation within LHON which may align more with NICE's preferred reference case.(90) However, EQ-5D is known to have poor convergence validity when used in visual disorders and DSU TSD 8 states that evidence from literature reviews suggest that EQ-5D is not appropriate for assessing the impact on some forms of visual impairment.(90,91) Therefore, given the inappropriateness of using EQ-5D scores to evaluate HRQoL within this appraisal, alternative methods were considered.(92)

Furthermore, whilst Lawrence *et al.* (a) developed the health states vignettes using individuals living with LHON (N=9) and clinical experts (N=5), the utility values were elicited using healthy members of the general population with no experience of visual impairment. This raises a substantial limitation in the utility values derived from this study.(86,87)

Therefore, given previous HTA appraisals for idebenone, the alignment of better-seeing eye utilities with the model structure and the limited available literature with suitable utility values conducted in patients with LHON, Brown *et al.* was considered the most appropriate alternative to inform HRQoL in this CEA. However, given the uncertainty in the differing utility sources, scenario analyses were conducted using utility values derived from Czoski-Murray *et al., Rentz et al.* and Lawrence *et al.* and are presented in B.3.11.3.

Table 30. Base-case utility values used in the CEA as derived from Brown *et al.* (1999)

Health state	Utility values
LogMAR <0.3	0.840
LogMAR 0.3-0.6	0.770
LogMAR 0.6-1.0	0.670
LogMAR 1.0-1.3	0.630
LogMAR 1.3-1.7	0.540
CF	0.520
HM	0.350
LP	0.350

Abbreviations: CF – Counting fingers; HM – Hand motion; LP – Light perception

B.3.4.5.2 Caregiver HRQoL

LHON has a major emotional and financial impact on families and carers of the patients.(7,93) As detailed in Section B.1.3.2, LHON impacts almost all aspects of patients' and caregivers' lives; activities of daily living, emotional functioning, relationships, studies, work, recreation and finances.(7) Due to the devastating nature of LHON to patients and the associated caregiver burden, it is essential to consider caregiver HRQoL in the base-case CEA and this is consistent with the NICE manual for health technology evaluations (2022).(56) UK clinical experts also agreed that it would be appropriate to model the impact of LHON on caregivers.(26)

Quantitative caregiver QoL was not collected in the clinical trials for idebenone and the literature on the disutility of caregivers of patients with LHON and other ophthalmological diseases is limited, despite the fact that the amount of unpaid care required increases as vision deteriorates. Therefore, caregiver disutilities are taken from HST 11, and are derived from a study by Wittenberg *et al.* 2013. (65,94)

Wittenberg *et al.* conducted a literature review to measure the disutility of caring for an ill or disabled family member.(94) Fifteen studies were included in the review, where 12 found measurable effects as large as -0.718. Illnesses studied included childhood disorders (e.g spina bifida, congenital malformations), diseases of the elderly (e.g Alzheimer's disease and dementia), physically disabling conditions (e.g arthritis, multiple sclerosis), and medical conditions such as cancer and stroke. Wittenberg *et al.* found that parents of children with activity limitations have a 0.08 lower EQ-5D score than parents of children without activity limitations. In HST 11, a disutility of 0.04 was selected on the basis that it was conservatively assumed that the disutility for carers of adults with the eye disease is half of that of carers of children.(65)

Given the mean age of patients in this CEA is 34 years, a similar approach to HST 11 was adopted and a disutility of 0.04 is applied to all individuals in the five most severe health states (Table 31).

Table 31. Caregiver disutility values used in the CEA

Health state	HST 11 (Wittenberg *et al.* 2013)
LogMAR <0.3	0
LogMAR 0.3-0.6	0
LogMAR 0.6-1.0	0
LogMAR 1.0-1.3	0.04
LogMAR 1.3-1.7	0.04
CF	0.04
HM	0.04
LP	0.04

Abbreviations: CF – Counting fingers; HM – Hand motion; LP – Light perception

Table 32 summarises the utility values included within the CEA base-case and scenarios.

Table 32. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Base-case				
Patient HRQoL – [Utility source]				
LogMAR <0.3	0.840	0.79,0.89	Section B.3.4.3.1.1, Page 99	Given previous HTA submissions for idebenone and the model structure of this CEA being based in the better-seeing eye, Brown *et al.* was considered the most appropriate source to inform HRQoL in the base-case. (23) Brown *et al.* collected TTO utility values for 325 patients with varying visual impairment. See B.3.4.3.1.1 for further details.
LogMAR 0.3-0.6	0.770	0.70,0.84		
LogMAR 0.6-1.0	0.670	0.57,0.77		
LogMAR 1.0-1.3	0.630	0.54,0.72		
LogMAR 1.3-1.7	0.540	0.43,0.65		
CF	0.520	0.36,0.68		
HM	0.350	0.10,0.60		
LP	0.350	0.10,0.60		
Caregiver HRQoL – HST 11				
LogMAR <0.3	0		Section B.3.4.5.1, Page 104	No QoL data were collected for caregivers within the clinical trials. Therefore, caregiver disutility values were derived from HST 11, where similar health states were used.
LogMAR 0.3-0.6	0			
LogMAR 0.6-1.0	0			
LogMAR 1.0-1.3	0.04			
LogMAR 1.3-1.7	0.04			
CF	0.04			
HM	0.04			
LP	0.04			

Abbreviations: CF – Counting fingers; HM – Hand motion; LP – Light perception; TTO – time-trade off

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was undertaken to identify cost and resource use studies for LHON. The SLR to identify cost and resource use was carried out under the same search as the economic SLR. A full breakdown and identified publications can be found in Section B.3.1. Full details of the SLR methods, strategies, inclusion and exclusion criteria and results are presented in Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs

B.3.5.1.1.1 Idebenone

Treatment costs for idebenone are calculated based on the three-monthly acquisition cost of treatment, multiplied by the compliance and persistence of idebenone. No administration costs are considered since idebenone is an oral treatment.

The dosing schedule for idebenone aligns with the SmPC.(24) The cost at list price for a 30-day supply (one pack of 180 tablets, 150 mg, two tablets three times per day) of idebenone is £6,364 and £[redacted] at PAS price. This is multiplied by three to give a three-monthly cycle cost of £19,370 at list price and £[redacted] at PAS price.

Compliance on treatment from the RHODOS study in the first six months was high: 96% in idebenone-treated patients. However, compliance data were not collected after 6-months in the RHODOS study or at any time point in the EAP study. RWE from an early access programme in France suggests that the compliance rate drops after the first six months: compliance for 0 to 5 months, 6 to 10 months, 11 to 15 months and 16 to 20 months were 107%, 87%, 75%, and 80%, respectively.(95) Therefore, it can be expected that the compliance rate in the EAP, for which clinical effectiveness is measured between 6 to 36 months, would be lower than 96%. Nevertheless, to remain conservative, a high compliance rate of 96% is used for all model cycles. Scenarios using 100% compliance and an average from the French RWE study are explored in the sensitivity analysis (B.3.11.3).

Persistence data that were available for idebenone from the RHODOS and EAP studies were considered to inform the duration of treatment with idebenone. The Kaplan Meier estimator of pooled persistence data from the studies (Figure 21) was considered up to three years, after which it was assumed that all patients will have discontinued treatment and aligns with the length of follow-up data provided for the transition probabilities.

Whilst persistence up to three years was assumed within the model, this can be considered a conservative assumption. Within the EAP study, treatment duration ranged from 2.4 – 70.4 months.(19) However, due to the limited number of patients with data beyond 36 months (N=19), modelling persistence beyond this timepoint in addition to clinical benefit via the transition probabilities would have caused uncertainties. Furthermore, UK clinicians consulted within the validation stated that patients would expect to be treated until they demonstrate a stabilisation in VA, which varies for all patients. Therefore, it was considered appropriate to model three years persistence in the CEA to limit the uncertainties within the data.

Figure 21: Kaplan Meier estimator of persistence on idebenone

For each cycle, the three-monthly cost of treatment (£[redacted] – PAS price) is multiplied by the compliance rate (96%) and cycle-specific persistence rate using the Kaplan Meier estimator to generate the treatment costs per cycle.

B.3.5.1.1.2 SoC

As detailed in Section B.1.3.4, there are no specific treatments or guidelines available in England that meet the therapeutic treatment goals in LHON. No other therapeutic treatments are licensed specifically for patients with LHON in England, and therefore the comparator is SoC in this CEA. SoC consists of established clinical management, which includes visual aids, occupational and low vision rehabilitation and lifestyle management (no smoking, reduced alcohol consumption, diet that includes fresh fruit and vegetables).

As detailed in Section B.3.2.3.2, SoC is captured within the model through resource use associated with each health state. Therefore, SoC costs are accumulated through the time spent in the various health states.

As resource use costs are also accumulated in the idebenone treatment arm, the CEA assumes that patients receiving idebenone also receive SoC.

B.3.5.2 Health state unit costs and resource use

The model includes resource use for LHON patients. Resource use inputs are based on health state rather than treatment arm. Resource use inputs have been informed by a key opinion leader (KOL) survey (2022) conducted by Chiesi and published literature, and subsequently validated by 5 UK clinicians in August 2023. (26,34) Resource input for ophthalmologist visits were informed directly by UK clinicians and differ between treatment arms for the first year (four cycles). After this, ophthalmologist visits are the same in both treatment arms in all health states (Table 33).(26) For further details on the KOL survey and UK validation interviews see Appendix N.

Resource use costs consist of medical and non-medical costs and are comprised of two aspects: visits to the neuro-ophthalmologist and the cost of blindness. The cost of blindness is made up of hospitalisation (due to injurious falls), outpatient care (low vision aids and rehabilitation in daily living), community care (blind registration and supportive living), residential care and the cost of depression resulting from LHON. Similar to what was seen in HST 11, the cost of residential care was only applied to patients over the age of 65 years. The cost of blind registration and depression resulting from LHON are only assumed to occur once over a patient's lifetime.

Resource use costs have been sourced from the National Schedule of Reference Costs 2021/2022 in the first instance. Where this was not possible, costs were valued using published literature. The cost of a neuro-ophthalmologist and hospitalisation were sourced from the National Schedule of Reference Costs 2021/2022.(96) The cost of outpatient care, community care (blind registration and supportive living), residential care and the cost of depression resulting from LHON were sourced from Meads *et al.* 2003 and inflated to the cost year 2022/2023 using the Unit Costs of Health and Social Care manual (2021), Personal Social Services Research Unit (PSSRU).(57,58) Previous NICE HTAs for aflibercept (TA294), ranibizumab (TA274) and ranibizumab plus pegaptanib (TA155) have also considered resources identified in Meads *et al.* using the NHS and PSS perspective. (68,69,97)

Table 33: Frequency of ophthalmology visits as informed by UK clinicians

	Unit cost (£)	Frequency		Source
		Idebenone	SoC	
Cyle 1-4 (per cycle)	143.93	0.75	0.25	Cost: NHS reference costs 2021/2022. Assumed to be the cost of outpatient care - Ophthalmology service, Non-Admitted Face-to-Face Attendance, Follow-up (WF01A) Input: Informed by UK clinicians
Cycle 5+ (per cycle)		0.25		

Table 34 presents resource use for costs for each health state.

Table 34. Resource use and unit costs inputs by health state

State	Unit cost (£)	Proportion of patients per cycle (%)	Source
Hospitalisation			
LogMAR <0.3	432.20	2%	Cost: Hospitalisation due to injurious falls. Based on the cost of A&E attendance, NHS reference costs 2021/2022: Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment (VB02Z)
LogMAR 0.3-0.6		3%	
LogMAR 0.6-1.0		10%	
LogMAR 1.0-1.3		18%	
LogMAR 1.3-1.7		20%	
CF		22%	
HM		27%	
LP		30%	
Outpatient care			
LogMAR <0.3	577.26	13%	Costs: Low vision aids and rehabilitation in activities for daily living. Meads *et al.*
LogMAR 0.3-0.6		38%	
LogMAR 0.6-1.0		80%	
LogMAR 1.0-1.3		83%	
LogMAR 1.3-1.7		83%	
CF		83%	
HM		83%	
LP		83%	
Community care – blind registration			
LogMAR <0.3	164.74	0%	Costs: Meads *et al.,* inflated to cost year 2022/23
LogMAR 0.3-0.6		25%	
LogMAR 0.6-1.0		78%	
LogMAR 1.0-1.3		100%	
LogMAR 1.3-1.7		100%	
CF		100%	
HM		100%	
LP		100%	
Community care – supportive living			
LogMAR <0.3		0%	

LogMAR 0.3-0.6	4,818.23	0%	Costs: Meads *et al.,* inflated to cost year 2022/23
LogMAR 0.6-1.0		20%	
LogMAR 1.0-1.3		40%	
LogMAR 1.3-1.7		48%	
CF		57%	
HM		63%	
LP		70%	
Residential care			
LogMAR <0.3	26,896.83	0%	Costs: Meads *et al.,* inflated to cost year 2022/23
LogMAR 0.3-0.6		2%	
LogMAR 0.6-1.0		7%	
LogMAR 1.0-1.3		7%	
LogMAR 1.3-1.7		8%	
CF		20%	
HM		22%	
LP		35%	
Depression resulting from LHON			
LogMAR <0.3	662.90	7%	Costs: Meads *et al.,* inflated to cost year 2022/23
LogMAR 0.3-0.6		20%	
LogMAR 0.6-1.0		30%	
LogMAR 1.0-1.3		33%	
LogMAR 1.3-1.7		42%	
CF		45%	
HM		58%	
LP		65%	

Abbreviations: CF – Counting fingers; HM – Hand motion; LHON – Leber's hereditary optic neuropathy; LP – Light perception

Within the UK clinician validation interviews, one clinician stated that whilst the current resource use estimates are plausible, they would expect to see an approximate times two increase in outpatient care resource use due to low vision clinics. To explore this uncertainty, a scenario has been presented in 0 exploring the impact of a times two increase in the proportion of patients utilising outpatient care.

B.3.5.3 Adverse reaction unit costs and resource use

As described in Section B.2.10 and Section B.3.4.4, AEs were not included in the CEA for either treatment arm and therefore no costs and resource use are applied.

B.3.5.4 Miscellaneous unit costs and resource use

The introduction of idebenone is expected to result in minimal changes, if any, to the way current services are run for patients with LHON in England, which has been validated by two UK clinicians. Whilst another three UK clinicians stated that there would be an expected increase in the frequency of clinic visits within the first year of treatment with idebenone, this increase has already been captured within the resource costs (Table 33).

B.3.5.4.1 Societal costs

LHON has a significant negative impact in diagnosed patients and their family. As such, in addition to direct costs, a scenario has been explored to consider the societal impact of LHON. This included the cost of informal care, the cost of unemployment and the cost of absenteeism (short-term disability leave). A breakdown of costs and inputs is provided in Appendix J.

B.3.6 Severity

Given the severity of the condition, there is a clear unmet need for effective treatments that improve the VA of patients with LHON. As the first licensed therapeutic treatment that demonstrates substantial clinical effectiveness, idebenone addresses this unmet need.

B.3.6.1 Severity modifier

In line with the NICE 2022 manual(56), the absolute and proportional QALY shortfall associated with the SoC of patients with LHON was calculated. Within the updated framework, differential QALY weights may be applied if the absolute or proportional shortfalls estimated lie within specified cut-off ranges (Table 35).

Table 35. QALY weightings for severity as per the NICE health technology evaluations manual

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
X1.7	At least 0.95	At least 18

Abbreviations: NICE – National Institute of Health and Care Excellence; QALY – Quality-adjusted life-year

To estimate the shortfall, the Schneider *et al.* (2021) estimator was used, which was cited by NICE as a potential option for calculating applicability of a severity modifier.(98) This tool uses ONS data from England to generate the general population survival with various sources of data to inform utility estimates. Given NICE DSU guidance indicates that directly collected EQ-5D-3L using the Health Survey for England (HSE) 2014 dataset is a preferred method of capturing utility values, the reference case data source in the Schneider et al tool, which uses directly collected EQ-5D-3L from the HSE 2014 dataset, was considered to represent the most recent and robust source for the base-case QALY shortfall calculations.

The QALY shortfall (QS) was calculated assuming a mean age of 34 years and 14% female (as per the RHODOS study, Table 36). The expected total QALYs for the general population were calculated using the Schneider *et al.* (98) tool reference case for general population utilities (MVH value set + HSE 2014 ALDVMM [Hernandez Alava, *et al.*]). The total expected QALYs for patients with the disease treated with current SoC was based on the modelled SoC arm of the Company base-case. The total expected QALYs in patients with the disease on current SoC were then compared to the general population QALYs to calculate the absolute and proportional shortfall (PS).

Table 36. Summary features of QS analysis

Factor	Value	Reference to section in submission
Sex distribution	14% female	Section B.3.3.1
Starting age	34 years	Section B.3.3.1

Abbreviations: QALY – Quality-adjusted life-year.

Based on the above, the absolute QS is estimated to be [redacted] and the PS is estimated to be [redacted]% (Table 37). The results show that this appraisal does not meet the threshold of a QALY weight of 1.2 for both AS and PS under the current NICE cut-off threshold criteria.

Table 37. Results of the QS analysis

General population QALY source	Expected total QALYs for the general population	Total discounted QALYs that people living with a condition would be expected to have with current treatment*	QALY shortfall	QALY weight*
Reference case: MVH value set + HSE 2014 ALDVMM [Hernandez Alava M, *et al.*]	13.85	[redacted]	Absolute: [redacted] Proportional: [redacted]%	1.0x

*All calculations based on the tool developed by Schneider *et al.*, 2021.(98)
Abbreviations: ALDVVM – Adjusted limited dependent variable mixture model; HSE – Health Survey for England; MVH – York Measurement and Valuation of Health; QALY – Quality-adjusted life-year.

As demonstrated, despite the extreme rarity and severe burden of LHON outlined above, idebenone does not currently qualify for the severity modifier. This may be due to the conservative assumption to not model the mortality benefit of patients with improved VA, and therefore, the mortality benefit that would be demonstrated in the idebenone arm is not captured.

However, LHON has a substantially severe burden on patients. Vision loss due to LHON has a major impact on patient wellbeing and affects almost all aspects of life, such as activities of daily living, emotional functioning, relationships, studies, work and recreation. It is exacerbated by the young age of symptom onset (6). This causes a substantial decrease in patient QoL. Furthermore, LHON is an ultra-rare disease with a prevalent population of approximately 975 patients in England and <300 of those patients affected by sight loss. (4,5)

Therefore, given that LHON is a very rare and severe disease that affects a young population including many patients under the age of 18 years old, Chiesi urge NICE to consider the severe impact LHON has on patients in England and the step change idebenone would present in the management of LHON.

B.3.7 Uncertainty

The model base-case has been informed by clinical expert opinion as well as external validation (see Section B.3.14 and Appendix N). Extensive sensitivity analyses have been performed to test the structural and parameter uncertainty with a summary of components and approaches provided in Table 38 (see Section **Error! Reference source not found.** for results). Scenario analyses have also been explored to examine the impact of uncertainty (Section 0).

Table 38. Summary of variables applied and tested in economic model

Component	Parameter grouping	Tested in OWSA?	Tested in PSA?	Testing in Scenario analysis?
Model settings	Time horizon			✓
	Discount rates			✓
Patient characteristics	Patient age	✓	✓	✓
	Percentage male	✓	✓	✓
	Baseline population data			✓
Utilities	Patient HRQoL	✓	✓	✓
	Caregiver disutility	✓	✓	✓
Costs	Compliance	✓	✓	
	Persistence	✓	✓	
	Resource use	✓	✓	✓
	Societal costs			✓

Abbreviations: HRQoL – Health-related quality of life; OWSA – One-way sensitivity analysis; PSA – Probabilistic sensitivity analysis

B.3.8 Managed access proposal

Chiesi consider the clinical and economic evidence presented within this submission to be a suitable basis for a routine commissioning decision.

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

Table 39 summarises the base-case variables and their measurement of uncertainty included in the CEA.

Table 39. Summary of base-case variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: [confidence interval] (distribution)	Reference to section in submission
Model specification			
Time horizon (years)	Lifetime – 66 years	N/A (fixed values)	B.3.2.2
Cycle length	3 months	N/A (fixed values)	B.3.2.2
Cost discount rate (%)	3.5	N/A (fixed values)	B.3.2.2
Health discount rate (%)	3.5	N/A (fixed values)	B.3.2.2
Patient characteristics			
Male (%)	86	[38%,100%] (BETA)	B.3.3.1
Age (years)	34	[31, 37] GAMMA	B.3.3.1
Efficacy			
Transition probabilities – idebenone	[See Section B.3.3.2.1]	N/A (fixed values)	B.3.3.2.1
Transition probabilities - SoC	[See Section B.3.3.2.2]	N/A (fixed values)	B.3.3.2.2
Utilities			
Total utility – LogMAR <0.3	0.84	[0.79, 0.89] (BETA)	B.3.4.5
Total utility – LogMAR 0.3-0.6	0.77	[0.70, 0.84] (BETA)	B.3.4.5
Total utility – LogMAR 0.6-1.0	0.67	[0.57, 0.77] (BETA)	B.3.4.5
Total utility – LogMAR 1.0-1.3	0.63	[0.54, 0.72] (BETA)	B.3.4.5
Total utility – LogMAR 1.3-1.7	0.54	[0.43, 0.65] (BETA)	B.3.4.5
Total utility – CF	0.52	[0.36, 0.68] (BETA)	B.3.4.5
Total utility – HM	0.35	[0.10, 0.60] (BETA)	B.3.4.5
Total utility – LP	0.35	[0.10, 0.60] (BETA)	B.3.4.5
Drug costs			
Compliance	96%	[N/A] (BETA)	B.3.5.1.1.1
Persistence	[See Section B.3.5.1.1.1]	N/A (fixed values)	B.3.5.1.1.1
Resource use and costs			

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: [confidence interval] (distribution)	Reference to section in submission
Ophthalmology visit – idebenone arm – cycles 1-4 - frequency	0.75	[0.49,1.07] (GAMMA)	B.3.5.2
Ophthalmology visit – SoC arm – cycles 1-4 - frequency	0.25	[0.16,0.36] (GAMMA)	B.3.5.2
Ophthalmology visit – cycle 5+ - frequency	0.25	[0.16,0.36] (GAMMA)	B.3.5.2
Proportion of patients - Hospitalisation - logMAR <0.3	2%	[1%,2%] (BETA)	B.3.5.2
Proportion of patients - Hospitalisation - logMAR 0.3-0.6	3%	[2%,5%] (BETA)	B.3.5.2
Proportion of patients - Hospitalisation - logMAR 0.6-1.0	10%	[6%,14%] (BETA)	B.3.5.2
Proportion of patients - Hospitalisation - logMAR 1.0-1.3	18%	[12%,26%] (BETA)	B.3.5.2
Proportion of patients - Hospitalisation - logMAR 1.3-1.7	20%	[13%,28%] (BETA)	B.3.5.2
Proportion of patients - Hospitalisation - CF	22%	[14%,31%] (BETA)	B.3.5.2
Proportion of patients - Hospitalisation - HM	27%	[17%,28%] (BETA)	B.3.5.2
Proportion of patients - Hospitalisation - LP	30%	[19%,42%] (BETA)	B.3.5.2
Proportion of patients - Outpatient care - logMAR <0.3	13%	[9%,19%] (BETA)	B.3.5.2
Proportion of patients - Outpatient care - logMAR 0.3-0.6	38%	[24%,54%] (BETA)	B.3.5.2
Proportion of patients - Outpatient care - logMAR 0.6-1.0	80%	[41%,99%] (BETA)	B.3.5.2
Proportion of patients - Outpatient care - logMAR 1.0-1.3	83%	[40%,100%] (BETA)	B.3.5.2
Proportion of patients - Outpatient care - logMAR 1.3-1.7	83%	[40%,100%] (BETA)	B.3.5.2
Proportion of patients - Outpatient care - CF	83%	[40%,100%] (BETA)	B.3.5.2
Proportion of patients - Outpatient care - HM	83%	[40%,100%] (BETA)	B.3.5.2
Proportion of patients - Outpatient care - LP	83%	[40%,100%] (BETA)	B.3.5.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: [confidence interval] (distribution)	Reference to section in submission
Proportion of patients - Community care - blind registration - logMAR <0.3	0%	[0%,0%] (BETA)	B.3.5.2
Proportion of patients - Community care - blind registration - logMAR 0.3-0.6	25%	[16%,35%] (BETA)	B.3.5.2
Proportion of patients - Community care - blind registration - logMAR 0.6-1.0	78%	[41%,99%] (BETA)	B.3.5.2
Proportion of patients - Community care - blind registration - logMAR 1.0-1.3	100%	[100%,100%] (BETA)	B.3.5.2
Proportion of patients - Community care - blind registration - logMAR 1.3-1.7	100%	[100%,100%] (BETA)	B.3.5.2
Proportion of patients - Community care - blind registration - CF	100%	[100%,100%] (BETA)	B.3.5.2
Proportion of patients - Community care - blind registration - HM	100%	[100%,100%] (BETA)	B.3.5.2
Proportion of patients - Community care - blind registration - LP	100%	[100%,100%] (BETA)	B.3.5.2
Proportion of patients - Community care - supportive living - logMAR <0.3	0%	[0%,0%] (BETA)	B.3.5.2
Proportion of patients - Community care - supportive living - logMAR 0.3-0.6	0%	[0%,0%] (BETA)	B.3.5.2
Proportion of patients - Community care - supportive living - logMAR 0.6-1.0	20%	[13%,28%] (BETA)	B.3.5.2
Proportion of patients - Community care - supportive living - logMAR 1.0-1.3	40%	[25%,56%] (BETA)	B.3.5.2
Proportion of patients - Community care - supportive living - logMAR 1.3-1.7	48%	[30%,67%] (BETA)	B.3.5.2
Proportion of patients - Community care - supportive living - CF	57%	[34%,78%] (BETA)	B.3.5.2
Proportion of patients - Community care - supportive living - HM	63%	[37%,86%] (BETA)	B.3.5.2
Proportion of patients - Community care - supportive living - LP	70%	[40%,93%] (BETA)	B.3.5.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: [confidence interval] (distribution)	Reference to section in submission
Proportion of patients - Community care - residential care - logMAR <0.3	0%	[0%,0%] (BETA)	B.3.5.2
Proportion of patients - Community care - residential care - logMAR 0.3-0.6	2%	[1%,2%] (BETA)	B.3.5.2
Proportion of patients - Community care - residential care - logMAR 0.6-1.0	7%	[4%,10%] (BETA)	B.3.5.2
Proportion of patients - Community care - residential care - logMAR 1.0-1.3	7%	[4%,10%] (BETA)	B.3.5.2
Proportion of patients - Community care - residential care - logMAR 1.3-1.7	8%	[5%,12%] (BETA)	B.3.5.2
Proportion of patients - Community care - residential care - CF	20%	[13%,28%] (BETA)	B.3.5.2
Proportion of patients - Community care - residential care - HM	22%	[14%,31%] (BETA)	B.3.5.2
Proportion of patients - Community care - residential care - LP	35%	[22%,49%] (BETA)	B.3.5.2
Proportion of patients - Depression resulting from LHON - logMAR <0.3	7%	[4%,10%] (BETA)	B.3.5.2
Proportion of patients - Depression resulting from LHON- logMAR 0.3-0.6	20%	[13%,28%] (BETA)	B.3.5.2
Proportion of patients - Depression resulting from LHON - logMAR 0.6-1.0	30%	[19%,42%] (BETA)	B.3.5.2
Proportion of patients - Depression resulting from LHON - logMAR 1.0-1.3	33%	[21%,47%] (BETA)	B.3.5.2
Proportion of patients - Depression resulting from LHON - logMAR 1.3-1.7	42%	[26%,58%] (BETA)	B.3.5.2
Proportion of patients - Depression resulting from LHON - CF	45%	[28%,63%] (BETA)	B.3.5.2
Proportion of patients - Depression resulting from LHON - HM	58%	[25%,80%] (BETA)	B.3.5.2
Proportion of patients - Depression resulting from LHON - LP	65%	[38%,88%] (BETA)	B.3.5.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: [confidence interval] (distribution)	Reference to section in submission
Ophthalmology visit cost (£)	143.93	[93,206] (GAMMA)	B.3.5.2
Hospitalisation cost (£)	1,728.82	[1119,2469] (GAMMA)	B.3.5.2
Outpatient care cost (£)	577.26	[374,825] (GAMMA)	B.3.5.2
Community care - blind registration cost (£)	658.96	[426,941] (GAMMA)	B.3.5.2
Community care - supportive living cost (£)	4,818.23	[3118,6882] (GAMMA)	B.3.5.2
Residential care cost (£)	26,896.83	[17406,38420] (GAMMA)	B.3.5.2
Community care - depression resulting from LHON cost (£)	2,651.60	[1716,3788] (GAMMA)	B.3.5.2

Abbreviations: CF – Counting fingers; HM – Hand motion; LP – Light perception

B.3.9.2 Assumptions

Table 40 summarises the key assumptions made within the CEA.

Table 40. Assumptions

Parameter	Assumption
Safety	
Idebenone	Idebenone has a benign safety profile, and therefore no incremental safety concerns compared to no treatment are expected. As detailed in Section B.2.10 and B.3.4.4, no AEs are applied in the CEA for the idebenone or SoC treatment arms.
SoC	
Survival	
Survival of patients with LHON	There is no additional probability of death due to LHON compared to the general population. Evidence exists demonstrating that the risk of mortality is higher in patients with blindness and visual impairment. Since idebenone can prevent blindness and reduces visual impairment, it can be expected that treatment with idebenone would be associated with a reduced mortality risk compared to no treatment. However, given the lack of specific mortality data for idebenone, the conservative assumption is made that there is no treatment effect on mortality associated with idebenone. Given this, a conservative assumption is also made that there is no treatment effect on mortality associated with SoC.
Quality of life inputs	
Utilities	Where utility data is not available from clinical trials for idebenone, utility values are derived from available literature and dependent on health state.

Carer disutilities	A carer disutility is applied, consistent with HST11, and is dependent on health state.
Costs and resource use	
Resource use inputs	It is assumed that resource use values associated with each health state differ, based on clinical expert opinion.
Compliance	Compliance data were not collected after 6-months in RHODOS or EAP. It is unlikely that the transitions of idebenone patients using EAP data past 6-months are based on a compliance rate of 96%. Indeed, RWE from an access programme in France suggests that the compliance rate does drop after the first 6-months: compliance for 0 to 5-months, 6 to 11-months, 11 to 15-months and 16 to 20-months were 107%, 87%, 75%, and 80%, respectively. Nevertheless, to remain conservative, a high compliance rate of 96% is used for all model cycles. (95)
Persistence	Kaplan-Meier estimator used to determine persistence with idebenone in England. This assumes all patients discontinue treatment by 3-years. However, this is considered to be a conservative assumption (See B.3.5.1.1.1 for further details).

Abbreviations: AE – Adverse event; CEA – cost-effectiveness analysis; EAP - Expanded access programme; HST - Highly specialised technology; LHON – Leber's hereditary optic neuropathy; RWE – real-world evidence; SoC – Standard of care

B.3.10 Base-case results

B.3.10.1 Base-case incremental cost-effectiveness analysis results

As mentioned in Section B.1.3, a confidential PAS has been submitted for PASLU approval. This arrangement is in the form of a simple PAS at [redacted] This PAS has been applied and the results presented reflect this discount. The base-case deterministic cost-effectiveness results for idebenone (at the PAS price) vs. SoC are presented in Table 41. The results demonstrate that, compared with SoC, idebenone is associated with QALY gains of [redacted]. Given that no survival benefit is assumed within the CEA, idebenone is not associated with any life years (LY) gains compared to SoC. This suggests a substantial improvement in QoL for patients with LHON. This benefit is associated with incremental costs of [redacted] per patient over a lifetime resulting in an ICER of £20,307.

Table 42 presents the net health benefit (NHB) at the £30,000/QALY willingness-to-pay (WTP) threshold. Results demonstrate that at a WTP threshold of £30,000/QALY, the NHB is positive at [redacted].

Table 41. Base-case deterministic results (idebenone PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,307

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; PAS – Patient access scheme; QALYs – Quality-adjusted life years; SoC – Standard of care

Table 42. Net health benefit (idebenone PAS price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £30,000 WTP threshold
SoC	[redacted]	[redacted]	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NHB – Net health benefit; PAS – Patient access scheme; QALYs – Quality-adjusted life years; SoC – Standard of care; WTP – Willingness-to-pay.

B.3.11 Exploring uncertainty

Varios sensitivity and scenario analyses are presented below to highlight the uncertainties.

B.3.11.1 Probabilistic sensitivity analysis

A probability sensitivity analysis (PC was completed in the CEA to explore uncertainty in the results. PSA involves drawing a value at random for each variable from its uncertainty distribution. This is performed for each parameter simultaneously and the resulting incremental results are recorded. This constitutes one 'simulation'. 1,000 simulations were performed, which each gave a distribution of incremental results, and consequently, an assessment of the robustness of the cost-effectiveness results. A table of inputs values, confidence intervals and distribution are presented in Table 39.

For event rates and utilities, a beta distribution was used to restrict draws to between 0 and 1. For costs and resource use estimates, a gamma distribution was fitted to prevent values less than zero. Treatment costs for idebenone remained fixed. An incremental cost-effectiveness plane (ICEP) scatter plot and cost-effectiveness acceptability curve (CEAC) were produced to graphically illustrate the level of variability and uncertainty in the results.

Table 43 summarises the results from the PSA using the PAS price of idebenone. In the PSA, using the PAS price, the ICER is £20,194 per QALY gained for idebenone vs. SoC. The incremental per patient costs with idebenone vs. SoC are £[redacted] and the incremental per patient QALYs gained are [redacted]. The results of each probabilistic model run are presented in the cost-effectiveness (CE) plane for idebenone and SoC (Figure 22). All iterations in the CE-plane are in the North-East quadrant demonstrating a positive QALY gain and confirming the clinical benefit of idebenone vs. SoC when parameter uncertainty is evaluated. Figure 23 and Figure 24 demonstrate the CEAC and the cost-effectiveness acceptability frontier using the PAS price.

Table 43. Mean PSA results (at the PAS price)*

Technologies	Total		Incremental		ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
SoC	[redacted]	[redacted]	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	20,194

***20% variati**on applied in the PSA, in the absence of SE or CIs.
Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; PAS – Patient access scheme; QALYs – Quality-adjusted life years; SoC – Standard of care

Figure 22. Cost-effectiveness plane - idebenone (at the PAS price) vs. SoC*

*20% variation is applied in the PSA in the absence of SE or CIs
Abbreviations: PSA – Probabilistic sensitivity analysis; QALY – Quality-adjusted life-year

Figure 23. Cost-effectiveness acceptability curve - idebenone (at the PAS price) vs. SoC*

*20% variation is applied in the PSA in the absence of SE or CIs
Abbreviations: PSA – Probabilistic sensitivity analysis; QALY – Quality-adjusted life-year

Figure 24. Cost-effectiveness acceptability frontier - idebenone (at the PAS price) vs. SoC*

*20% variation is applied in the PSA in the absence of SE or CIs
Abbreviations: PSA – Probabilistic sensitivity analysis; QALY – Quality-adjusted life-year

B.3.11.2 Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted to test the impact of individual parameters when their values are set to the lower and upper limits of the confidence intervals whilst all other parameters are maintained at the base-case setting.

Table 44 and Figure 25 present the ICERs and the tornado plot showing the 10 parameters which had the largest impact on the ICER.

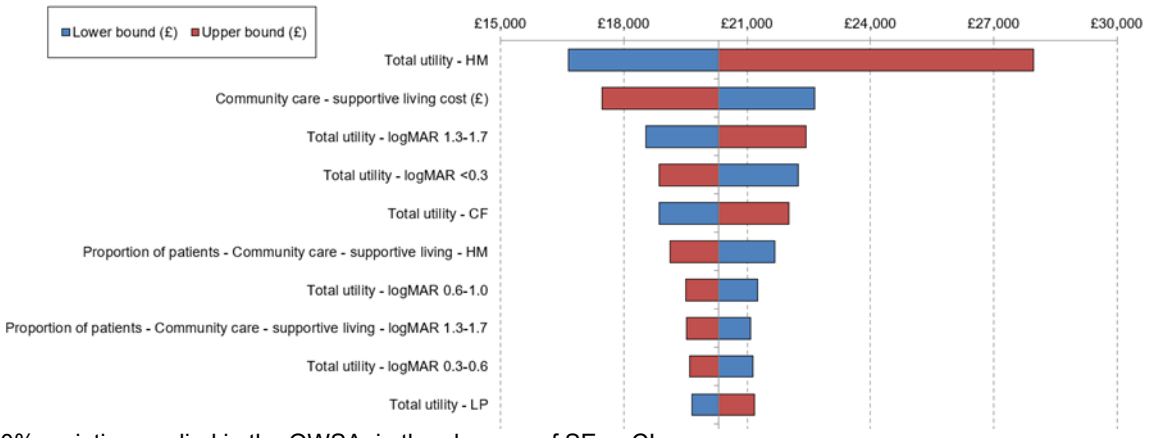
The total utility for the hand motion health state had the largest impact on the ICER followed by the cost of supportive living and the total utility for the LogMAR 1.3-1.7, LogMAR <0.3 and CF health states. Other parameters had a lower impact on the ICER when varied between their upper and lower bounds.

Table 44. OWSA results (idebenone [at the PAS price] vs. SoC)*

Parameter	ICER at lower bound (£)	ICER at upper bound (£)	Difference (£)
Total utility - HM	16,652	27,971	11,318
Community care - supportive living cost (£)	22,650	17,462	5,188
Total utility - logMAR 1.3-1.7	18,541	22,444	3,903
Total utility - logMAR <0.3	22,243	18,868	3,374
Total utility - CF	18,868	22,008	3,140
Proportion of patients - Community care - supportive living - HM	21,677	19,132	2,545
Total utility - logMAR 0.6-1.0	21,255	19,499	1,756
Proportion of patients - Community care - supportive living - logMAR 1.3-1.7	21,080	19,524	1,556
Total utility - logMAR 0.3-0.6	21,148	19,606	1,542
Total utility - LP	19,655	21,184	1,530

*20% variation applied in the OWSA, in the absence of SE or CIs.
Abbreviations: CF – Counting fingers; HM – Hand motion; ICER – Incremental cost-effectiveness ratio; logMAR – Logarithm of the minimum angle of resolution; LP – Light perception; OWSA – One-way sensitivity analysis; PAS – Patient Access Scheme; SoC – Standard of care

Figure 25. Tornado plot showing OWSA results on the ICER (idebenone [at the PAS price] vs. SoC)*



*20% variation applied in the OWSA, in the absence of SE or CIs.
Abbreviations: CF – Counting fingers; HM – Hand motion; ICER – Incremental cost-effectiveness ratio; logMAR – Logarithm of the minimum angle of resolution; LP – Light perception; OWSA – One-way sensitivity analysis; PAS – Patient Access Scheme; SoC – Standard of care

B.3.11.3 Scenario analysis

Scenario analyses were performed to test key structural and inputs assumptions. A PSA was run for all scenarios where all parameters are assigned probability distributions and varied jointly under a given scenario. The results of probabilistic scenario analyses are presented in Table 45. PSAs for all scenarios were run for 1,000 iterations. The largest deviations from the base-case ICER came from the discount rates for cost and outcomes set to 0% and 6%.

Scenarios exploring the impact of different utility sources, the baseline characteristics and distribution sources, caregiver disutility, the compliance rate, and the inclusion of amendments to the resource use input remained similar to the base-case ICER demonstrating how the economic results are robust to changes in key model outputs.

Table 45. Scenario analysis (probabilistic results – idebenone [at the PAS price] vs. SoC)

Parameter	Scenario number	Base-case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
Base-case probabilistic results				[redacted]	[redacted]	**20,462**
Discount rate for costs and outcomes	1	3.5%	0%	[redacted]	[redacted]	2,929
	2		1.5%	[redacted]	[redacted]	9,964
	3		6%	[redacted]	[redacted]	34,074
Time horizon	4	66 years	50 years	[redacted]	[redacted]	21,375
	5		30 years	[redacted]	[redacted]	29,754
Utility source	6	Brown *et al.* (1999)	Rentz *et al.* (2014)	[redacted]	[redacted]	18,787
	7		Lawrence *et al.* – EQ-5D-5L	[redacted]	[redacted]	22,070
	8		Lawrence *et al.* – HUI3	[redacted]	[redacted]	15,680
	9		Lawrence *et al.* – TTO	[redacted]	[redacted]	18,714
	10		Czoski-Murray *et al.*	[redacted]	[redacted]	20,094
Baseline characteristics source	11	RHODOS	EAP	[redacted]	[redacted]	20,333
	12		CaRS	[redacted]	[redacted]	19,224
	13		Pooled RHODOS, EAP and CaRS	[redacted]	[redacted]	19,484
Caregiver disutility	14	Included	Excluded	[redacted]	[redacted]	22,181
Compliance	15	RCT compliance	Full compliance – 100%	[redacted]	[redacted]	21,453
	16		RWE compliance – 87%	[redacted]	[redacted]	17,454
Resource use inputs	17	Informed by KOL survey (2022) with the exception of ophthalmologist visits	Base-case + outpatient care use adjusted according the UK clinical input	[redacted]	[redacted]	21,615

*20% variation applied in the PSA, in the absence of SE or CIs.
Abbreviations: CI – confidence intervals; CaRS – Case record survey; EAP – Extended access programme; NHS – National Health Service; PSA – probability sensitivity analyses; PSS – Personal social services; RWE – Real-world evidence; SE – standard error

B.3.12 Subgroup analysis

Due to the rarity of LHON and the limited patient number from clinical trials, no subgroup analyses were performed in or considered relevant for the CEA. Chiesi consider this appraisal should be based on the full anticipated licensed population.

B.3.13 Benefits not captured in the QALY calculation

The QALY calculation in the economic modelling will consider the costs and benefits of idebenone in patients for the treatment of vision loss due to LHON. However, due to the severe impact of LHON on patients and caregivers, it is also expected that the introduction of idebenone is likely to result in substantial benefits outside of the QALY calculation.

B.3.13.1 Benefits of the technology to government bodies other than the NHS

As stated in Section B.1.3.2, LHON is associated with a profound burden to patients and caregivers. LHON mostly presents in young adults, typically in the second and third decades of life (29), at a time when patients are expected to be in full-time employment or beginning their careers. Patients with LHON may also have young families to support. The disease often causes patients to work reduced hours, for lower wages and can encourage early retirement, all which contribute to productivity losses.(7,34)

Furthermore, as detailed in Section B.1.3.2 and in Section B.3.4.5, LHON has a substantial impact on caregivers of patients and it affects almost all aspects of their life; activities of daily living, emotional functioning, relationships, studies, work, recreation and finances.(7) In a recent study by Williams *et al.* (2023)(93), qualitative findings reported a substantial burden for many carers and family members of patients with LHON. In a KOL survey conducted by Chiesi (2022)(34), clinicians reported that the percentage of patients needing informal caregiver support and the number of days a caregiver is needed are both increased with increasing LogMAR values. As with patients with LHON, this disease can cause caregivers to work reduced hours which contributes to productivity losses. This was validated by UK clinicians.

The impact of LHON on both patients and caregivers means that families of patients with LHON are likely to require financial assistance to cover child tax benefits, disability allowance, carer allowance and modifications to the home. This financial assistance is provided by various UK governmental bodies, including the Departments for Work and Pensions, Education, Health and Social Care, and Communities, as well as Local Government and County Councils. By improving patient outcomes and therefore reducing the family need for governmental financial support, idebenone will generate savings to UK governmental bodies.

As well as the financial burden that LHON has on UK government bodies, the productivity losses of patients and caregivers has a great indirect cost to society. This includes the cost of informal care, patient unemployment and absenteeism from work (see Appendix J). Whilst it is sometimes difficult to capture the true impact of these losses, the Company ran a societal perspective scenario to explore the impact these indirect costs have on the ICER (see Appendix J for the results of the probabilistic societal scenario). The scenario produced a dominating ICER per QALY for idebenone, with incremental savings of £[redacted], demonstrating the substantial impact idebenone has on the cost to society. By improving patient outcomes, and therefore reducing the need for informal care and allowing patients and caregivers to continue to work or increase their working hours, idebenone generates a reduction to indirect costs.

B.3.13.2 Out-of-pocket savings to patients and caregivers

As detailed in Section B.1.3.2 and above, patients with LHON and their caregivers are likely to suffer big financial challenges in terms of out-of-pocket costs. Home adaptations and assistive devices may be needed for patients with LHON. Whilst some of these costs are borne by the NHS, some may not be. In the NICE appraisal (HST 18) for an analogous disease (metachromatic leukodystrophy (MLD)), it was noted that families self-fund £30,000 for home modifications, £13,200 per year for specialist care, and over £16,000 on other items to support the child (99). Similar self-funding may be expected for families affected by LHON.

By providing meaningful benefits to patients, idebenone may reduce patient out-of-pocket costs associated with LHON.

B.3.14 Validation

B.3.14.1 Independent technical cost-effectiveness model QC

The cost-effectiveness model was quality assured by a senior health economist not involved in the model build who reviewed the model for coding errors, inconsistencies, and plausibility of inputs and outputs. The model was also subject to stress testing of extreme scenarios to test for technical modelling errors and plausibility of results.

B.3.14.2 Expert validation of cost-effectiveness analysis

Clinical validation was sought for the cost-effectiveness analysis consisting of UK expert clinical validation. A full description of methods and responses of the UK validation are given in Appendix N.

B.3.14.3 External validation

The economic analysis for idebenone conducted as part of this appraisal is the first CEA in LHON in England specifically. However, this economic analysis has undergone numerous other European HTAs, including SMC, AWMSG and NCPE, and therefore has had thorough external validation. (15,16,55)

The validity of SoC as the comparator for this appraisal has been validated by UK clinicians. UK clinicians also agreed that the clinical effectiveness data used within the model demonstrates meaningful benefit of treatment with idebenone. Furthermore, UK clinicians agreed that the defined health states used in the model structure were appropriate for capturing the clinical and economic burden of LHON and that the inputs were plausible for decision making (Appendix N).

B.3.15 Interpretation and conclusions of economic evidence

The CEA developed as part of this appraisal is relevant to patients aged 12 years and above with LHON who are expected to use idebenone in England. UK clinical experts agreed that that treatment with idebenone is suitable in all patients with LHON, across acute and chronic populations. The clinical data informing the CEA are primarily taken from the randomised, double-blind, placebo-controlled, multicentre RHODOS trial in which patients had vision impairment in at least one eye due to LHON. Long-term clinical data was supplemented using the real-world EAP and CaRS studies. Baseline characteristics were in line with RHODOS, the primary RCT for idebenone. UK clinical experts agreed that the patient population of RHODOS and EAP studies used in the economic analysis were generalisable to the UK population.

In addition to the CEA being relevant to UK patients, it is also reflective of clinical management of LHON in England. Given the ultra-rare nature of LHON, there are currently no specific treatments or guidelines available in England that target the underlying disease. Patients are currently treated with a range of clinical management, including visual aids, occupational and low vision rehabilitation and lifestyle management, which make up the SoC of LHON. UK clinical experts validated the CEA inputs related to SoC management, which were informed using a Chiesi conducted KOL survey (2022) (Appendix N).(34)

The CEA developed as part of this NICE appraisal is an adaptation of the CEA presented in other UK HTA appraisals for idebenone and has undergone extensive validation. (15,16,55)

Additionally, Chiesi would like to highlight that idebenone would provide a step change in the management of LHON as the first and only licensed treatment for patients with this severely disabling and ultra-rare disease in England. Whilst idebenone does not currently qualify for the severity modifier, vision loss due to LHON has a substantially severe impact on patient and carer QoL. Therefore, idebenone is key in transforming the care of patients with LHON in England.

The CEA confirms that idebenone is expected to generate transformative and substantial clinical and economic benefits to patients with LHON. In the base-case, idebenone is expected to generate [redacted] additional QALYs at an incremental cost of £[redacted], resulting in an ICER of £20,307, within NICE's threshold of £30,000.

In line with the guidance from the NICE manual (2022), uncertainty has been extensively explored. The robustness of base-case results was assessed through probabilistic, deterministic, and scenario analyses with results demonstrating the stability of the base-case with a high level of certainty:

- PSA was performed to explore the joint parameter uncertainty. The probabilistic results are consistent with the deterministic results with a probabilistic QALY gain of [redacted] at an incremental cost of £[redacted], resulting in a probabilistic ICER of £20,194. Idebenone, at PAS price, has a [redacted]% chance of being cost-effective at a WTP threshold of £30,000/QALY gained.

- Parameter uncertainty was evaluated through OWSA. The analysis showed that the CE results are most sensitive to the total utility of the hand motion health state and the cost of supportive living. Other parameters had a lower impact on the ICER when varied between their upper and lower bounds. All results consistently showed that idebenone (at PAS price) is a cost-effective at a WTP threshold of £30,000.

- A range of probabilistic scenario analyses were performed to evaluate key model assumptions and alternative choices of inputs to test the robustness of the base-case results. The model was most sensitive to the discount rate on costs and outcomes.

Whilst developing a robust CEA in a in ultra-rare disease is challenging, the CEA for this appraisal has a number of strengths:

The CEA framework has undergone extensive validation by other HTA bodies, including SMC, AWMSG and NCPE. Furthermore, UK clinical experts agreed that the model structure and health states fully capture the clinical and economic burden of LHON.

The CEA resource use costs and inputs have been informed by KOLs and validated by UK clinical experts.

Key clinical inputs for the CEA are taken from the RHODOS trial, the pivotal, randomised, double-blind, placebo-controlled, multicentre clinical trial.

Despite the steps taken to develop a robust model, the CEA has limitations:

- LHON is ultra-rare with very limited data in the literature. The model therefore uses data from proxy diseases and previous HTA's to inform inputs. Inputs based on alternative disease areas or more generic vision loss studies were validated by UK clinicians.

Only 85 patients across idebenone and placebo treatment arms in RHODOS, 87 patients in the idebenone arm in the EAP study and 74 patients in the CaRS were included in the CEA. Whilst this may still present a large percentage of patients with LHON, it is a low sample size for the CEA and means there may be high heterogeneity in outcomes observed.

The primary RCT for idebenone, RHODOS, only had a 24-week duration. UK clinical experts agreed that 24 weeks was not long enough to demonstrate a significant difference in the primary endpoint. Therefore, in order to accurately demonstrate a patient's clinical progression over a sufficient time frame within this CEA, the RHODOS clinical data was pooled with follow-up studies. For the idebenone arm, the EAP study was used to inform clinical progression from 23 weeks onwards. In the SoC arm, the CaRS was used to inform clinical progression from 24 weeks onwards.

The clinical studies and CEA outlined in this submission has established idebenone as the first targeted therapy to demonstrate a substantial clinical and economic benefit for patients with LHON. Idebenone offers in improvement in QoL for patients, caregivers and families in a setting where there is a substantial unmet need.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547]

Summary of Information for Patients (SIP)

October 2023

File name	Version	Contains confidential information	Date
ID547_Idebenone_LHON_SIP_26Oct2023	1.0	No	26th October 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Response: **Active ingredient**: Idebenone **Brand name**: Raxone®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Response: Idebenone is indicated for the treatment of visual impairment in adolescent and adult patients with Leber's hereditary optic neuropathy (LHON).(1)

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response: Idebenone was first granted a marketing authorisation (MA) by the European Medicines Agency (EMA) on the 08th September 2015.(2) As a result of Brexit, the EU licence for idebenone, which has an existing centrally authorised product (CAP) MA, was subjected to grandfathering process and was issued with a Great Britain Product Licence (PLGB) MA number effective from 1st January 2021.(3) The application for Orphan Drug Designation Transfer has been submitted, receiving a positive opinion from the EMA and is currently awaiting the final European Commission (EC) decision.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response:
Chiesi have supported through our grants program the work of the Lily Foundation (mitochondrial disease charity), the LHON Society and the Royal National Institute for the Blind (RNIB). Activities supported have included general support for their organisation overheads as well as specific projects such as a LHON society family support event, a 'Living Well with sight-loss' courses, educational events, printing of educational books for children, a safeguarding policy review and partial support for a clinical research fellowship.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Response:

LHON is an ultra-rare, maternally inherited disease which causes rapid loss of vision

LHON is an ultra-rare maternally inherited disease which causes sudden visual impairment. LHON is caused by a genetic mutation which affects the ability of cells to produce the energy needed for them to function. These mutations damage the retinal ganglion cells of the eye, the cells responsible for vision. The resulting damage leads to a progressive loss of eyesight.(4)

There are three primary genetic mutations (m.11778G>A, m.14484T>C, m.3460G>A) and other rarer mutations which can cause this inherited form of blindness.(5) Carrying a LHON mutation predisposes you to developing symptoms of LHON and the peak age for this is ages between 15 to 30 years but it can occur at any age. Factors such as smoking, excessive alcohol intake, head trauma, psychological stress, occupational exposure to chemical toxins and nutritional deficiencies have been linked as triggers for vision loss in LHON.(6–9) It is estimated that there are approximately 289 symptomatic patients with LHON in England.

LHON usually starts with painless blurring of vision in one eye, with the second eye following a similar course usually within weeks to months. The condition worsens over time, resulting in blindness in around 97% of people with LHON, typically within one year from the initial display of symptoms.(2,4,10) The comparative image between normal vision and LHON vision is presented in Figure 1.

Figure 1. Comparative image of the visual field between normal vision and LHON vision

Normal vision LHON vision

Adapted from: Santhera Pharmaceuticals AG. Data on file: PharSolution. Raxone® Pharmacotherapeutic Report, 2017.(11)
Abbreviation: LHON – Leber hereditary optic neuropathy

LHON is associated with significant burden to patients

LHON typically manifests in young adults during the prime of their lives. Therefore, vision loss due to LHON has a major impact on patient wellbeing and affects almost all aspects of life including daily living, emotional functioning, relationships, studies, work and recreation.(12,13) Sudden vision loss can have a profound impact on the quality of life of LHON patients.(14) Patients often struggle to cope in the weeks and months following their diagnosis and report difficulties in activities of daily living, such as reading small print, newspapers, book or recognising faces.(15,16) Research conducted in the UK also revealed significant psychological distress that LHON patients often suffer, including having suicidal thoughts, depression and anxiety, clearly demonstrating the severe impact of LHON. (17)

There is a substantial burden for families and caregivers of patients with LHON

LHON has a significant impact on caregivers. LHON affects almost all aspects of caregivers' lives; activities of daily living, emotional functioning, relationships, studies, work, recreation and finances.(12) Caregivers are deeply involved in LHON patients' lives, often rearranging personal activities around patients' needs, sometimes sacrificing their own pursuits.(12) The caregiving responsibilities can also lead many caregivers to reduce their working hours or stop working completely.(12) Parents, partners and even siblings have to dedicate more time and effort to the patients daily living activities such as dressing, meals, shopping and transport often resulting in increased physical and mental tiredness of the caregiver. Caregivers often describe their situation as generating stress, anxiety and worry about the patient's future.(12,13,18)

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?
Response: Diagnosis of LHON is usually based on patient and family medical history, neuro-ophthalmological (brain-eye) examination and genetic testing. LHON should be suspected if patients present with the following characteristics; male gender, age between 15 and 30 years, painless vision loss, one eye affected initially, followed by second eye within weeks to months, positive family history, swelling of the optic disc and thickening of the retinal nerve layer.(7) To confirm a definitive diagnosis of LHON and rule out other conditions that may resemble LHON symptoms, patients with suspected LHON may undergo a series of tests, including a magnetic resonance imaging and specific eye tests. The diagnosis of suspected LHON is usually confirmed by genetic testing.(4)

Given the above, the diagnosis of LHON can be a lengthy process (19). It can take an average of over 7 months from onset of symptoms to receiving a confirmed diagnosis for LHON.(6,19)

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Response:

There are currently no specific treatments available in England and patients are currently managed with lifestyle management and supportive care, known as standard of care.

Based on the risk factors outlined in **Section 2a,** patients should avoid tobacco, alcohol, exposure to drugs and toxins. Patients may also receive supportive treatments for LHON, which include the use of nutritional supplements which aim to reduce the stress on your mitochondria and provide alternative energy source. Other supportive measures such as low vision aids and near-infrared light therapy may also be used to assist patients with severe vision loss.(20)

Patients can also receive genetic counselling which can help them adapt to being diagnosed with a genetic condition such as LHON. It can help them understand what it means for them and their family, including what it could mean to any children they may have.(21)

Standard of care, as described above, does not, however, tackle the underlying genetic condition of LHON, nor does it prevent vision loss or aid in its recovery. Its benefits for patients remain limited, highlighting a significant unmet medical need in the management of LHON.(20)

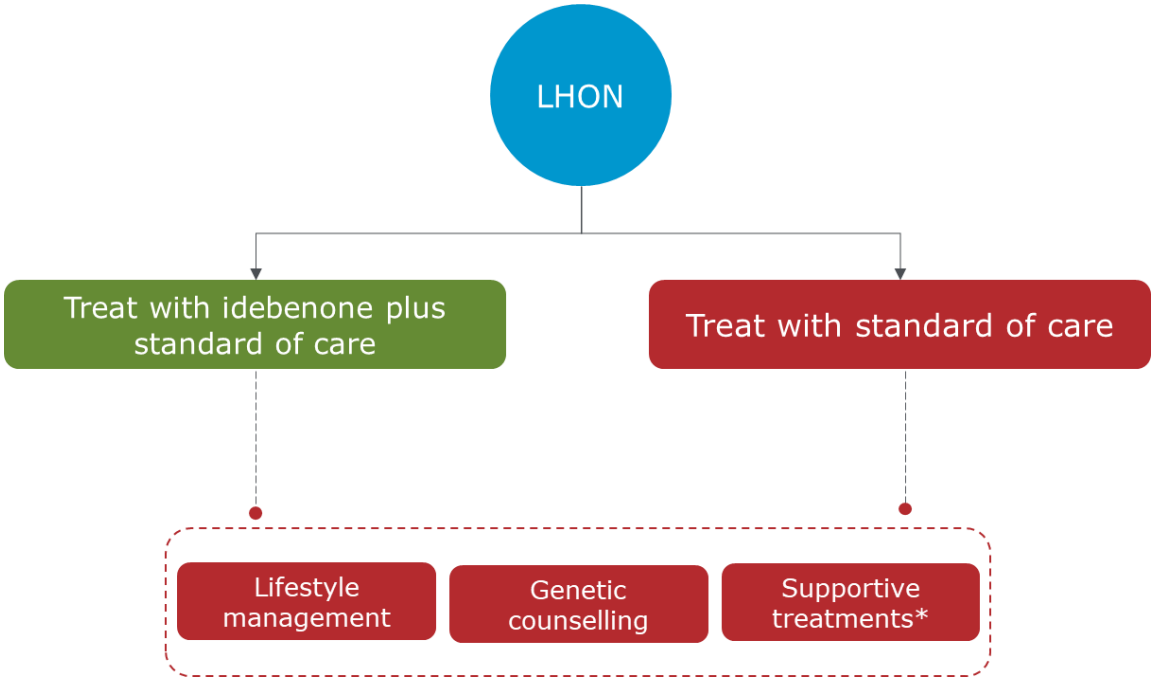
Idebenone would present a step change in the management of LHON as the first and only licensed treatment for patients with LHON in England as current supportive treatments available for LHON patients do not prevent vision loss or allow recovery of visual function.(2,20)

Idebenone has demonstrated the potential to reactivate viable-but-inactive retinal ganglion cells in LHON across the three primary genetic mutations as well as other rarer LHON-causing mutations (2). The effectiveness of idebenone has been documented up to 5 years after onset in controlled studies and up to 50 years after onset in open-label and case series studies.(2,14,22,23,23–28)

LHON is a disease associated with high humanistic and economic burden for both patients and informal caregivers. Therefore, the introduction of idebenone has the potential to provide significant life-changing benefits to carers as it could restore a degree of autonomy to LHON patients and reduce the burden on caregivers.(18)

Therefore, the proposed placement in the treatment pathway is as a first-line treatment for LHON patients, as shown in Figure 2.

Figure 2. Proposed management of LHON



*Supportive treatments include nutritional supplements, low vision aids, and near-infrared light therapy.(20)
Abbreviations: LHON – Leber's hereditary optic neuropathy

As a consequence of no current established clinical practice for the treatment of LHON in the NHS, idebenone remains the only potential treatment for LHON patients.(29) Therefore, idebenone will be introduced as a first-line treatment.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:

LHON can cause significant lifetime morbidity as affected patients will remain disabled and blind in most cases for the rest of their lives.(2,4)

LHON is a debilitating condition which significantly impacts patients' quality of life, surpassing the impact of other eye conditions.(16) In a study published in 2009, Kirkman and colleagues measured the quality of life of LHON patients by interviewing patients using a Visual Function Index (VF-14) questionnaire. The VF-14 was developed to formally assess functional limitations caused by eye diseases. It is a widely accepted validated tool that accurately measures a person's capability to perform daily activities that are reliant on normal vision.(16) The VF-14 score indicates the level of visual function and ranges from 0 (worst level of visual function) to 100 (best level of visual function). The study reported that patients with LHON have a visual function score of 25, whereas patients with other eye disorders - for example, age-related macular degeneration (eye condition

that generally affects older people) have a visual score of 89 and patients with low vision have a score of 54-62. The authors concluded that LHON has a severe negative impact on quality of life and has the greatest impact on visual function compared to the other eye disorders.(16)

A study by Combal *et al*. 2015 that interviewed patients with LHON demonstrated the detrimental impact of the disease on patient's quality of life. A total of eight face-to-face semi-structured group interviews were conducted. Four with patients and four with caregivers were conducted in each studied country; USA, UK, Germany and France.(12,13) All interviewed patients, including those recently diagnosed with some retained central vision, stress that they felt locked in a world apart, that was gloomy and shapeless, and that their vision loss made identification of people, objects and situations very complicated as demonstrated in Figure 3 below.(12,13) LHON also affects almost all aspects of caregivers' lives as described in **Section 2a.**

Figure 3. LHON patients' quotes, extracted from interviews conducted by Combal *et al.*

Source: Combal *et al.* (2014)(13)

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:

Overview of idebenone:

- The Summary of Product Characteristics (SmPC) for idebenone can be found here: https://www.medicines.org.uk/emc/product/2269/smpc#gref
- A patient information leaflet for idebenone is available here: https://www.medicines.org.uk/emc/product/2269/pil#about-medicine

LHON is caused by a genetic mutation which affects the ability of cells to produce the energy needed for them to function. These mutations damage the retinal ganglion cells of the eye, the cells responsible for transmitting signals from the eye to the brain. The resulting damage leads to a progressive loss of eyesight.(30) Any treatment that improves or maintains the patient's condition and improves vision would be a significant advancement in the management of LHON. Idebenone is one such drug that has shown the potential to reactivate viable-but-inactive retinal ganglion cells in LHON patients. Through this biochemical mode of action, idebenone can therefore promote recovery of vision in patients who experience vision loss.(2) The benefits of idebenone in all LHON

patients regardless of mutation types are demonstrated, and has efficacy documented up to 5 years after onset in controlled studies and up to 50 years after onset in open-label and case series studies. (2,14,22,23,23–28)

The current standard of care for LHON, as described in **Section 2c**, does not tackle the underlying genetic condition of LHON, nor does it prevent visual function loss or aid in its recovery. Its benefits for LHON patients remain limited.

Idebenone is therefore highly innovative as it is the only treatment for visual impairment in adolescents and adults with LHON. Idebenone has the potential to alleviate the severe burden of LHON on patients by preventing and recovering vision loss and improve the quality of life of patients and carers.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Response:
No. Idebenone is not intended to be used with any other medicines in this indication.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Response:
Idebenone is an oral therapy. Each tablet contains 150mg idebenone.(1) The recommended dose is two tablets, three times a day, and this is a total of six tablets per day. It is recommended to take the tablets with food as this helps to get more of the medicine from your stomach into your blood. Swallow the tablets whole with a glass of liquid.(31)

Idebenone, being an oral therapy, offers convenience to patients as it does not require frequent hospital visits and does not require too much dependence on caregivers.

Patients should stay on idebenone until stabilisation of visual acuity.(32)

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Response:

The key clinical data most relevant to this appraisal are the RHODOS, RHODOS-OFU, Expanded Access Programme (EAP) and the LEROS trial. Information on each study is provided below.

RHODOS(22,33)

Title: 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 (SNT-II-003) [NCT00747487]

Objective: To determine whether administration of idebenone can improve visual function in patients with LHON

Location: Munich (Germany), Newcastle (United Kingdom) and Montreal (Canada)

Population: LHON patients between 14 and 64 years old

Patient group size: N=85

Comparators: Placebo

Inclusion criteria: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 5 years or less prior to baseline; 4) Confirmation of either G11778A, T14484C or G3460A LHON mitochondrial DNA 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 child-bearing potential)

Exclusion criteria: 1) Treatment with Coenzyme Q10 or idebenone within 1 month prior to baseline; 2) Pregnancy and/or breastfeeding 3) Weekly alcohol intake 35 units (men) or 24 units (women); 3) Current drug abuse; 4) Clinically significant abnormalities of clinical haematology or biochemistry including, but not limited to, elevations greater than two times the upper limit of normal AST, ALT or creatinine; 5) Participation in another clinical trial of any investigational drug within 3 months prior to baseline; 6) Other factor that, in the investigator's opinion, excluded the patient from entering the study

Primary efficacy endpoint: Best recovery of logMAR visual acuity in either right of left eye

Completion date: February 2010

RHODOS-OFU(24,34)

Title: A single-visit, observational, follow-up study of patients with Leber's Hereditary Optic Neuropathy following participation in SNT-II-003 trial (SNT-II-003-OFU) [NCT01421381]

Objective: To examine the change in visual acuity of patients who had previously participated in the RHODOS trial, and compare the current VA with that observed at baseline and after 24 weeks of treatment in the RHODOS trial

Location: Munich (Germany), Newcastle (United Kingdom) and Montreal (Canada)

Population: LHON patients between 15 years to 69 years

Patient group size: N=60

Comparators: No treatment (previously randomised to placebo in RHODOS)

Inclusion criteria: Previous participation in RHODOS trial

Exclusion criteria: No exclusion criteria

Primary efficacy endpoint: Change in best visual acuity compared to Visit 2/baseline and Visit 5/Week 24 or last treatment visit of RHODOS

Completion date: December 2011

Expanded Access Programme(14)

Title: Expanded Access Programme

Objective: To provide access to idebenone to individual "named" LHON patients at the request and under the personal care of a registered physician according to applicable local regulations. The objective was to describe the EAP patient population and report on clinical outcomes and safety, after ongoing long-term treatment with idebenone in clinical practice.

Location: Germany, United Kingdom, Australia, New Zealand, Poland, Sweden, Spain, Turkey, Switzerland and the United States of America

Population: Genetically confirmed LHON and disease duration of less than 12 months since the onset of vision loss (most recently affected eye)

Patient group size: N=111

Comparators: None

Inclusion criteria: A diagnosis of LHON with confirmed LHON mitochondrial DNA mutation type and onset of vision loss in the second eye less than 12 months prior to the data of the baseline visit

Exclusion criteria: None

Study endpoints:

- Clinically relevant recovery in visual acuity from nadir: defined as visual acuity improvement from "off-chart" to at least five letters "on-chart", or "on-chart" improvement of at least 10 letters.
- Clinically relevant stabilisation of visual acuity: defined as maintenance of visual acuity <1.0 logMAR in those with a visual acuity <1.0 logMAR at baseline.

Completion date: June 2018

LEROS(35)

Title: External natural history controlled, open-label intervention study to assess the efficacy and safety of long-term treatment with Raxone in Leber's hereditary optic neuropathy (LHON)(SNT-IV-005)[NCT02774005]

Primary Objective: To assess the efficacy of idebenone in the promotion of recovery or stabilisation of visual acuity in patients treated with idebenone ≤1 year after the onset of symptoms, compared to a matched external natural history control group of idebenone-naïve patients.

Location: The United States of America, Austria, Belgium, Bulgaria, Germany, Italy, Poland, Portugal, Spain, United Kingdom

Population: Patients with LHON age ≥ 12 years with onset of symptoms ≤ 5 years from baseline. Patients much also have a confirmed diagnosis of either G11778A, T14484C or G3460A LHON mtDNA mutations

Patient group size: N=199

Comparators: None

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

Exclusion criteria: 1) Patient had provided natural history data to the CaRS (SNT-CRS-002); 2) Any previous use of idebenone; 3) Any other cause of visual impairment; 4) Known history of clinically significant elevations (greater than three times the upper limit of normal) of AST, ALT or creatinine; 5) Any condition which in the investigator's opinion may have put the patient at significant risk, confounded study results or interfered significantly with the patient's participation in the study 6) Participation in another clinical trial of any investigational drug within 3 months prior to baseline 7) Hypersensitivity to the active substance or to any of the excipients listed in the smPC; 8)Women who were pregnant or who had a positive pregnancy test at the baseline visit; 9) Women who were breastfeeding

Primary endpoint: Proportion of eyes with clinically relevant recovery of visual acuity from baseline or in which baseline visual acuity better than 1.0 logMAR was maintained at month 12 in patients treated with idebenone ≤1 year after the onset of symptoms, compared to the matching external natural history control group. Clinically relevant recovery (CRR) was defined as a change from "off-chart" VA to a value of at least 1.6 logMAR or an improvement of at least 0.2 logMAR within "on-chart.

Completion date: March 2021

Abbreviations: AIDS – Acquired immunodeficiency syndrome; ALT – Alanine aminotransferase; AST – Aspartate aminotransferase; CaRS – Case record survey; LHON – Leber's hereditary optic neuropathy; mtDNA – Mitochondrial deoxyribonucleic acid

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

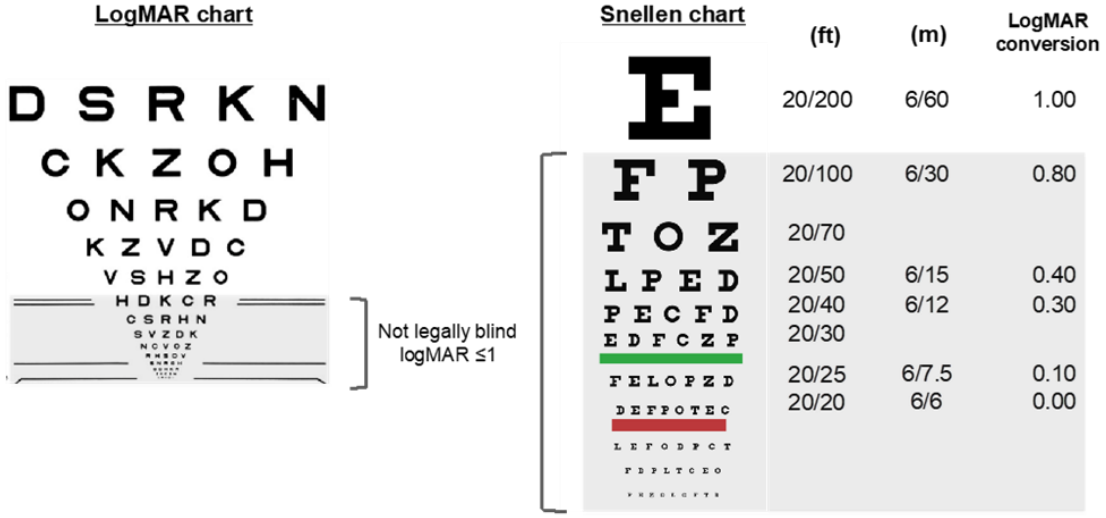
In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Response:

Visual acuity was a commonly used outcome across studies. To understand the efficacy of idebenone, it is important to detail how visual acuity is measured by an eye specialist. Visual acuity, which relates to the sharpness of vision, is measured by reading down an eye chart.

Typically, eye specialists use either the logMAR chart, also known as the ETDRS (Early Treatment Diabetic Retinopathy Study) chart or the Snellen chart to assess visual acuity as shown in Figure *4* below.

Figure 4. Example of the logMAR (also known as the ETDRS chart) and Snellen chart



Note on the Snellen chart: The first number given is the distance in metres from the chart when sitting to read it. Usually this is a 6 (for 6 metres) but would be three if the person being tested were to sit closer to the chart (3 metres away).
Source: Santhera Pharmaceuticals AG (2016)(30)
Abbreviation: LogMAR – Logarithm of the minimum angle of resolution

Observers are required to read the chart from a distance. The results from the charts are then translated into the logMAR (logarithm of the minimum angle of resolution) scale, which quantifies visual acuity based on the number of letters an observer can read on the chart.(30,36)

LogMAR quantifies a large range of visual abilities, for example:

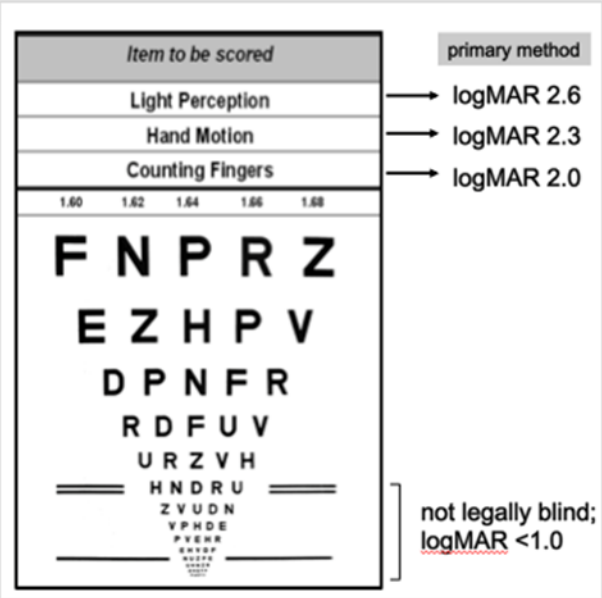
- A score of 0.0 means the observer has a normal vision.
- A score of 1.68 means the observer is unable to read any letter on the chart, and able to read only one large letter correctly at 1 metre distance.

A logMAR score of 1 or more represents legal blindness.

LHON patients are also classified as having 'off-chart' visual acuity if they are unable to read any letters on the chart. Therefore, to further assess LHON patients with progressively worsened vision,

they are scored based on their ability to count fingers (CF) from a distance of 30cm, detecting hand motion (HM) or light perception (LP) see
Figure **5**).(2,30,37)

Figure 5. The logMAR scale showing the 'off-chart' visual acuity categories



LogMAR values are assessed using the ETDRS charts(2)
Source: Santhera Pharmaceuticals AG (2016) (30)
Abbreviation: LogMAR – Logarithm of the minimum angle of resolution

The main measure of effectiveness was improvement in vision, mostly based on the numbers of letters patients were able to read on the eye test chart.

Results from RHODOS, RHODOS-OFU, the EAP and LEROS demonstrate that there is a consistent clinical benefit of treatment with idebenone across multiple trials. The positive results from RHODOS have been validated through confirmatory studies. The consistency of these results provides strength and validity to the findings of the primary and secondary endpoint analyses in RHODOS.

RHODOS(22,33)

Primary efficacy endpoint: best recovery of logMAR visual acuity between baseline and Week 24 in either right or left eye

- This endpoint measured either best improvement in VA between baseline and Week 24, or where neither eye improved, the change in VA represented the least worsening.
- Idebenone showed an improvement in vision compared to placebo over the study period of 24 weeks.(2)
- By the end of the study, patients in the idebenone group were able to read on average six letters more than at the beginning of the study, while those in the placebo group could read just one more letter on the eye chart.(2)
- Although the difference, between the idebenone and placebo group, was not statistically significant, this may have been because the trial did not last long enough (24 weeks) to show a significant difference, as supported by UK clinicians.(32)

Main secondary efficacy endpoint: change in best visual acuity at Week 24 compared to baseline

- This endpoint measured the best eye at Week 24 compared to the best eye at baseline.
- The change in best visual acuity may be the most relevant to the impact of the disease on a patient, being the closest related to visual function in daily life. (2)
- For change in best visual acuity at 24 weeks, patients in the placebo group had a decline of visual acuity by six letters (which means they could read on average six fewer letters on the eye chart) between baseline and Week 24. On the other hand, patients in the idebenone group showed a slight improvement where they could read on average, an additional one more letter on the eye chart.(2)

RHODOS-OFU(24,34)

Primary efficacy endpoint: change in best visual acuity

- This endpoint measured the best eye at Week 24 compared to the best eye at baseline.
- Best visual acuity at the RHODOS-OFU visit at Week 132 was slightly worse than at baseline in patients in the placebo group where patients had difficulty reading on average, an additional letter on the eye chart. However, best visual acuity improved in the idebenone group, where they were able to read on average, additional six letters on the eye chart.(2,11)
- The benefit of idebenone was maintained in this off-medication period (i.e. after Week 24 of the RHODOS trial) between treatment groups from baseline in RHODOS to RHODOS-OFU favouring idebenone.(24,37)

Key secondary endpoint: change in visual acuity of both eye and change in visual acuity of the best eye

- This endpoint measured the improvement in VA between baseline and Week 24 in both eyes and the best eye.
- The mean change in visual acuity of individual eyes from baseline of RHODOS to the RHODOS-OFU study visit at Week 132 showed a statistically significant difference between treatment groups in favour of the idebenone group, where patients in the idebenone group could read 11 more letters on the eye chart compared to the placebo group.(24)

Expanded Access Programme(14)

Clinically relevant recovery in visual acuity from nadir

- This endpoint measured best improvement in VA from when VA in an individual eye reaches its lowest point.
- The proportion of patients with recovery and the magnitude of recovery increased with treatment duration on idebenone.

Clinically relevant stabilisation of visual acuity

- This endpoint measured the maintenance of VA <1.0 logMAR in those with a VA <1.0 logMAR at baseline.
- 50% of patients at the last visit demonstrated an improvement in their ability to read, on average, an additional nine letters on the ETDRS chart with idebenone treatment compared to baseline.
- Compared with the natural disease course, early idebenone treatment provides an opportunity to prevent severe vision loss over a timespan when further visual acuity deterioration would be expected for most patients.

LEROS(35)

Primary endpoint: proportion of eyes that achieved a clinically relevant benefit

- Clinically relevant benefit (either a prevention of severe vision loss or a recovery of lost vision) was observed in 42.3% of eyes from LEROS patients compared to 20.7% eyes from natural history patients.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease-specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Response:

Patient-related quality of life impact of idebenone

Health-related quality of life data, specifically the EQ-5D-5L (a generic instrument measuring health-related quality of life), was not collected in studies for idebenone as it has been shown that the EQ-5D-5L is not a sensitive measure in eye conditions and therefore alternative instruments were considered.(38,39)

The RHODOS study collected health-related quality of life data in terms of change in Visual Function Index (VF-14), Clinical Global Impression of Change (CGIC) and energy levels using the Visual Analogue Scale (VAS). The VF-14 was also used in the RHODOS-OFU study.

- The VF-14 is a brief questionnaire designed to measure functional impairment on patients, originally intended to measure functional impairment caused by cataracts.(40) The VF-14 score indicates the level of visual function and ranges from 0 (worst level of visual function) to 100 (best level of visual function). (16)
- The CGIC is a 3-item observer-rated scale that measures global improvement or change in illness experience.(41)
- The VAS are psychometric response scales used to quantify subjective characteristics or attitudes. A VAS is usually a 100-mm long horizon line with word anchors at each end to express the extremes of feeling. Respondents mark a point on the line to indicate their level of experience. The distance from the marked point provides a quantitative measure.(42)

The overall difference between idebenone and placebo groups in change of VF-14 score at 24 weeks follow-up was not statistically significant. Similar findings were reported in the RHODOS-OFU. The change from baseline in CGIC scores was determined at 24 weeks, with no statistical analysis reported. Patient energy levels were assessed by VAS from baseline to Week 24 and both treatment groups reported minimally elevated energy levels.

The health-related quality of life instruments used in the RHODOS and RHODOS-OFU studies, however, cannot be translated into utility values (health state preference values). Utility values can take a value from 0 to 1, where 0 indicates death, and 1 indicates full health. In the absence of quality of life data from the clinical trials, utility values have been taken from Brown *et al.* 1999.(43) This large study collected time-trade off utility values in the better-seeing eye for patients across a range of logMAR scales and off-chart (i.e. hand motion, CF and LP) visual acuities.(43)

- A time-trade-off is a choice-based method of eliciting health state utility that a person is experiencing.
- Members of the general population were asked to judge scenarios in which they could live with fewer years of perfect health or more years in one of the health state (e.g. how many years in perfect health is equivalent to 10 years in the walking with assistance health state?).

In the Brown *et al.* 1999 study, improvements in patients' vision were reflected in higher utility values, indicating an enhancement in their quality of life as measured by logMAR visual acuity health

states. Given the paucity of quality of life data in LHON, the utilities presented in this study are assumed to be representative of LHON patients in England.

Caregiver quality of life impact of idebenone

Quantitative caregiver quality of life data was not collected in clinical trials for idebenone and the literature on disutility of caregivers (the impact on carer quality of life) of patients with LHON is limited, despite the fact that the amount of unpaid care required increases as vision deteriorates. Therefore, caregiver disutilities were taken from a previous NICE appraisal (HST11) related to a different eye condition, based on a study by Wittenberg *et al.* 2013.(44,45) Wittenberg *et al.* 2013 conducted a literature review to measure the disutility of caring for an ill or disabled family member. Illnesses studied included childhood disorders, diseases of the elderly, physically disabling conditions, and medical conditions such as cancer and stroke. Wittenberg *et al.* 2013 found that parents of children with activity limitations have a lower utility score than parents of children without activity limitations. Given that idebenone can prevent further vision loss and promotes recovery of vision in LHON patients, caregivers' quality of life is expected to improve after the patients are treated with idebenone.

Patient preference information:

Due to the rarity of LHON, there is no information on patient preference or willingness to accept side effects to receive the benefit of idebenone.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Response:

Idebenone has a consistent long-term safety profile and is well tolerated by LHON patients, as demonstrated in all three studies.(2,14,22,24) This was further validated by UK clinicians who expressed no notable safety concerns regarding idebenone.(32)

According to the patient information leaflet for idebenone:(31)

- Very common side effects (affect more than 1 in 10 people) of idebenone include: nasopharyngitis (cold) and cough.
- Common side effects (may affect up to 1 in 10 people) of idebenone include: diarrhoea (mild to moderate that usually does not require discontinuation of treatment) and back pain.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

Response:

- Idebenone is the first and only licensed therapy for the treatment of visual impairment in adolescent and adult patients with LHON.
- The current standard of care which consists of an extensive list involving lifestyle management (avoiding tobacco, alcohol, exposure to drugs and toxins), and genetic counselling do not prevent visual function loss or aid in its recovery.(20)
- Idebenone will therefore provide significant clinical benefits to patients as idebenone has shown potential to reactivate viable-but-inactive retinal ganglion cells in LHON patients. Through this biochemical mode of action, idebenone can therefore promote recovery of vision in patients who experience vision loss.(2)
- Given the improvement in vision in LHON patients, idebenone is expected to improve patients' quality of life, and daily living.
- By improving patients' quality of life and daily living, idebenone will potentially alleviate the substantial caregiver burden of looking after a patient with LHON.
- Idebenone, being an oral therapy, offers convenience to patients as it does not necessitate frequent hospital visits and does not require excessive dependence on caregivers.
- Idebenone has an established safety profile and was well tolerated in clinical studies. No dose adjustment is required for special populations and there are no additional monitoring requirements.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

No key disadvantages of using idebenone were identified for patients, caregivers, or their communities when compared to the current standard of care for LHON patients.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?

- How the condition, taking the new treatment compared with current treatments affects your quality of life.

For a treatment to be reimbursed by the NHS, the manufacturer must provide an economic model (also called a cost-effectiveness model) to demonstrate that the treatment will provide value for money and is therefore a good use of NHS resources. An overview of the economic model for idebenone in patients with LHON is provided below.

How the model reflects the condition

- The health economic model compares visual acuity, quality of life and costs across the lifetime of patients with LHON treated with idebenone compared with current standard of care.
- The model consists of eight health states based on visual acuity, as measured by the ETDRS logMAR chart to reflect the typical disease course of patients with LHON. The health states are the following (from "best" to "worst"): (i) logMAR<0.3, (ii) logMAR ≥0.3 and <0.6, (iii) logMAR ≥0.6 and <1.0, (iv) logMAR ≥1.0 and <1.3, (v) logMAR ≥1.3 and <1.7, (vi) Counting Fingers [CF], (vii) Hand Motion [HM] and (viii) Light Perception [LP]. Patients that die transition to death state.
- Two cohorts enter the model across the eight health states based on the baseline demographics of patients in the RHODOS study.(22) One cohort received idebenone while the other receives no treatment (standard of care). For each cohort, patients that die transition to the death state and surviving patients transition between the logMAR health states.
- Each health state is associated with specific healthcare resource use and costs, survival and quality of life (referred to as "utility").

Modelling how much a treatment extends life

- Given the lack of specific mortality data for idebenone, the conservative assumption is made that there is no treatment effect on mortality associated with idebenone. A conservative assumption is also made that there is no treatment effect on mortality associated with standard of care.

Modelling how much a treatment improves quality of life

- A patient's quality of life is expected to improve as idebenone has been shown to prevent blindness and increases the likelihood of having a clinically relevant response.(2,14,22,24)
- To determine quality of life in the economic model, utility values are taken from a Brown *et al*.(1999) study, conducted in patients who have vision loss.(43)
- Quantitative caregiver quality of life was not collected in the clinical trials for idebenone. Therefore, caregiver disutilities (the impact on caregiver quality of life) were sourced from a previous submission (HST11) related to a different eye condition based on a study by Wittenberg *et al.* 2013.(44,45) Wittenberg *et al.* conducted a literature review to measure the disutility of caring for an ill or disabled family member.

Modelling how the costs of treatment differ with the new treatment

- The current standard of care consists of established clinical management, which includes visual aids, occupational and low vision rehabilitation, and lifestyle management (no smoking, reduced alcohol consumption, diet that includes fresh fruit and vegetables).
- Standard of care is captured within the model through resource use associated with each health state. Therefore, standard of care costs is captured through the time spent in the various health states.
- In addition to costs associated with current management, patients treated with idebenone incur a three-monthly acquisition cost of treatment. No administration costs are considered as idebenone is an oral treatment.

Uncertainty

- LHON is a rare disease with limited published data.
- Given the above, there are uncertainties in the health economic model. Every effort has been made to reduce the impact of those uncertainties, including discussion and validation of the economic model approach and assumptions with UK clinical experts.
- Key uncertainties include:
    - Due to the lack of long-term randomised control trial (RCT) data, beyond 6-month real world evidence was used to fill the information gap.
    - No utility data was available from the RCT, hence published literature proxy data utility values were used.

Cost-effectiveness results

- Over a patient's lifetime, idebenone is expected to generate additional quality-adjusted life years (QALYs) compared to standard of care. One QALY is equivalent to one year of perfect health. This highlights the clear gain in quality of life compared with standard of care.

Additional factors

- LHON has a substantially severe burden on patients. Vision loss due to LHON has a major impact on patients' wellbeing and affects almost all aspects of life, such as activities of daily living, emotional functioning, relationships, studies, work and recreation. This is exacerbated by the young age of symptom onset. (12,13) This causes a substantial decrease in patient quality of life.
- Furthermore, LHON is an ultra-rare disease.
- Therefore, idebenone is the only hope that patients and caregivers have of meaningful improvements in outcomes and quality of life.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:

LHON is caused by a genetic mutation which damages the retinal ganglion cells of the eye, the cells responsible for transmitting signals from the eye to the brain. The resulting damage leads to a progressive loss of eyesight.(30) Through the available clinical evidence package, idebenone has demonstrated potential to reactivate viable-but-inactive retinal ganglion cells in LHON patients. Through this biochemical mode of action, idebenone can therefore promote recovery of vision in patients who experience vision loss.(2) The benefits of idebenone in all LHON patients, regardless of mutation types, are demonstrated, and has efficacy documented up to 5 years after onset in controlled studies and up to 50 years after onset in open-label and case series studies (2,14,22,23,23–28).

There are currently no licensed treatments for patients with LHON. Idebenone is therefore highly innovative as it is the first and only treatment for visual impairment in adolescents and adults with LHON. Idebenone therefore represents a "step change" for patients with LHON and their families.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
Response: No equality issues are anticipated for idebenone in this indication. Idebenone should be made available to all eligible LHON patients in the UK.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Response: • What is LHON? Available here: https://www.chiesiusa.com/rare-diseases/pipeline/leber-s-hereditary-optic-neuropathy/ • Chiesi press release 2023. Available here: https://www.chiesi.com/en/chiesi-group-announces-closing-of-licensing-transaction-with-santhera-for-an-orphan-drug-in-lhon/ • RHODOS clinical trial. Available here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3170530/ • RHODOS-OFU study. Available here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3572931/ • EAP study. Available here: https://pubmed.ncbi.nlm.nih.gov/32991388/ Further information on NICE and the role of patients: • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in health technology assessments Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-

content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

- **Clinical Global Impression of Change (CGIC):** 3-item observer-rated scale that measures global improvement or change in illness experience.
- **Clinically relevant recovery (CRR):** a measure that identifies clinically meaningful maintenance of visual acuity.
- **Clinically relevant stabilisation (CRS):** a measure that identifies clinically meaningful maintenance of visual acuity.
- **EuroQol-5 Dimensions 5-Levels (EQ-5D-5L):** EQ-5D-5L is a tool to measure the quality of life (QoL) of a person, based on their response to questions covering mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. EQ-5D is NICE's preferred QoL measure and is scored from a scale of 0–1, with 1 denoting perfect health.
- **Logarithm of the minimal angle of resolution (logMAR):** a logarithmic scale for assessing visual acuity.
- **Mitochondrial deoxyribonucleic acid (mtDNA):** the DNA located in mitochondria.
- **Quality-adjusted life year (QALY):** The QALY is a standardised unit of measure of the state of health of a person or group in which remaining years of life are adjusted to reflect the QoL during those remaining years of life. One QALY is equal to 1 year of life in perfect health.
- **Randomised controlled trial (RCT):** An RCT is a study in which a number of similar people are randomly assigned to two (or more) groups to test a specific drug, treatment or other intervention.
- **Utility:** The measure of the preference or value that an individual or society gives a particular health state. Utility is usually scored from 0–1, with 1 reflecting perfect health.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547]

Clarification questions

[November 2023]

File name	Version	Contains confidential information	Date
ID547 idebenone clarification letter PM for company	1.0	Yes	28/11/2023

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Comparative Effectiveness Data

A1. Priority question. The EAG is critically concerned that the company has not included the results of an indirect treatment comparison between idebenone and no intervention to inform the economic model to inform comparative treatment effectiveness after 6 months, i.e., when RHODOS RCT data are no longer available. The EAG notes the company did conduct a form of matched control analysis for a subgroup of patients within the LEROS trial, but the EAG considers this analysis to be inappropriate. Please clarify the following aspects of the matching algorithm used in the LEROS matched control analysis:

a) Please clarify why eyes were matched rather than patients?

As demonstrated in RHODOS, a patient's eyes often have a highly discordant onset, progression, and response to treatment.(1) More than two thirds of patients have a sequential onset, so over the first year of the disease this asymmetry in visual acuity (VA) between eyes is evident. Each eye shows a rate of progression and depth of the

nadir (worst detected VA) which is independent of the contralateral eye. It is well known, too, that in some cases, eyes can have some spontaneous improvement of the VA. This has one immediate consequence: on the one hand some eyes can show spontaneous improvement while the contralateral eye is still deteriorating, and this second eye does not necessarily follow the same progression or degree of nadir and/or recovery as the contralateral. The implications for the evaluation of potential efficacy of any therapeutic intervention, if only the best VA in a patient is assessed, are that this may miss an important recovery of one of the eyes and/or a prevention of further deterioration of the contralateral eye. In other words, one could be considering a lack of efficacy because the best VA has stayed unchanged while there could have been an important recovery in one of the eyes, allowing the eye to have a better binocular vision (this translates into better quality of life and independence).

Another consequence of considering patient best VA and not independent eyes, is that due to the sequential nature of the disease onset, one eye could be classified as chronic, while the most recent eye could just have the onset and be classified as subacute phase. When evaluating efficacy in terms of time to intervention, it would be difficult to consider this patient as just “subacute” or just “chronic”.

When defining the efficacy criteria of LEROS and based on the experience gathered through the clinical development of idebenone, it was considered necessary to evaluate eyes independently, as this could better profile the disease stage and detect any potential therapeutic effect.

b) Whether, for any patient, only a single eye was matched.

In some patients, only one eye was affected. In others, one eye's baseline was within the analysis timeframe, while the other was not. For example, when analysing eyes with a symptom onset of one year, if one eye had an onset of two years, we could only account for one eye in the analysis.

c) How the correlation between outcomes within an individual patient were accounted for in the analyses when two eyes from each patient were included?

This correlation was not accounted for.

d) Please clarify if the "the average time since onset of symptoms at Baseline calculated for LEROS" used for matching was mean or median.

The mean was used for the average time since onset.

e) In the matching algorithm for the primary endpoint it is stated that "Since there was no treatment to be considered in the NH control set, in principle any VA observation at any time point after the onset of symptoms in any eye could be used as a baseline for that eye. The primary outcome measure in LEROS was the VA at 12 months after BL. Therefore, using a "window" of ± 3 months, any eye with a VA observation at any time point in the NH control set which had a follow-up VA assessment within 12 ± 3 months was retained for use as a possible Baseline observation."

Given the natural disease course of Leber's hereditary optic neuropathy (LHON) including a subacute phase involving the rapid deterioration of VA to a nadir, followed by a relatively more stable long-term period, please clarify how "in principle any VA observation at any time point after the onset of symptoms in any eye could be used as a baseline"?

To better understand this statement, we need to highlight that the primary endpoint was evaluated at 12 months of treatment initiation. For the natural history cohort (for which there is no treatment received), those eyes that had a known symptom onset and a disease course of one year or less, could qualify as potential match.

As with treated eyes in LEROS where a subacute/dynamic eye could have a baseline visit any time between the symptom onset and the 1-year mark, this also applies to the NH control eyes. So, for any given natural history eye, any observation collected between symptom onset and the 1-year mark, could be considered as baseline.

Usually, recent onset patients (or eyes) are seen more often during the initial stages of the disease (e.g., monthly, weekly, quarterly, etc., depending on the routine clinical practice of the neuro-ophthalmologist). This results in several baseline visits potentially qualifying as "baseline". While in the LEROS eyes, baseline is clearly related to the initiation of treatment, in the NH cohort, there is no treatment to help in defining a baseline. This is the reason for the mentioned statement about "several potential baseline visits".

In order to improve the matching process, however, a subsequent condition is required (for the primary endpoint): NH eyes must have a follow-up visit after an interval of 12+/-3 months from the previous one considered as potential baseline. Logically, due to the frequency of visits in this early stage of the disease, there are potentially several visits fulfilling the last criteria, and thus, several corresponding baseline visits.

To further improve the matching process, other conditions are established:

- Only one visit can be selected as baseline.
- This potential baseline visit will be that one closest to the mean time since onset calculated for the LEROS eyes.
- In case of several potential baseline visits, the one occurring first is selected. For any eye that still has more than one visit pair, select the pair which time frame between 2 visits is closer to 12 month and occurs first in time.

f) Please clarify why, for the matched control patients, "the VA observation for which time since onset of symptoms was closest to the average time since onset of symptoms at baseline calculated for LEROS (see 2) was selected as the baseline VA observation for that eye."

The EAG is concerned that this procedure does not match control patients to the LEROS idebenone treated patients, but instead selects control patients at a similar time since symptom onset to the population average of LEROS. This will create a relatively homogenous time since symptom onset in the matched control cohort, even if the idebenone cohort was very heterogeneous. For analyses of these "matched"

cohorts to be unbiased, the EAG considers the following implausible assumptions would have to hold:

- **There is no interaction between time since onset and treatment effectiveness AND;**
- **Time since onset is the only prognostic factor in LHON, i.e., there is no other measured or unmeasured confounding.**

Please see the answer in part e for an explanation of the matching criteria agreed with the EMA. This was designed to as best as possible mimic a placebo-controlled study with the issues described above with the frequency of the eligible observations.

The natural history of both untreated LHON & LHON treated with idebenone is highly variable. Both eyes of a patient effectively act independently in terms of timings & degree of response and there is good evidence to demonstrate that whilst time since onset is a factor, very chronic patients, decades from onset can respond so again, the impact of time since onset is variable. This comes back to what is believed to be the mode of action of idebenone in that it can re-activate viable but dormant retinal ganglion cells. These viable RGC's would appear to remain in this state for many years.

A2. Priority question. Given the concerns raised in question A1, the EAG considers the matching procedure used by the company in the LEROS trial to be flawed and at very high risk of bias.

Please use a propensity score matched or propensity score weighted analysis (or any other alternative method for the comparative analysis of IPD following the guidance of NICE DSU TSD17) analysis using:

a) The full LEROS – Intent-to-treat (ITT) population and full CaRS dataset;

b) The subset of idebenone treated patients from these populations ≤1 year after onset of symptoms.

In this analysis, please match individual patients rather than eyes, to mirror the structure of the economic model where patients rather than eyes are modelled. Please ensure all prognostic factors, including but not limited to:

mtDNA mutation; time since symptom onset; age at symptom onset and baseline visual acuity (VA), are considered for matching.

Please compare the baseline characteristics of each matched cohort at baseline and report the following results:

- **Best recovery of logMAR visual acuity in either right or left eye;**
- **Change in best VA;**
- **CRR;**
- **Tables of transition probabilities between logMAR health states by visit.**

A response to A2 will be shared on 12th December.

Natural history

A3. Using the full data set from CaRS I and CaRS II and the placebo arm of RHODOS please provide an estimate of spontaneous recovery for LHON patients. Please provide appropriate regression analyses investigating the relationship between spontaneous recovery and: i) mutation status, ii) age at symptom onset, iii) time since symptom onset, iv) VA at nadir.

A response to A3 will be shared on 12th December.

Systematic literature review

A4. Please clarify why non-interventional studies were excluded from the real world evidence (RWE) SLR when the main comparator in the current appraisal is no pharmacological intervention and all of the long-term effectiveness studies provided in the submission did not include a control arm, other than (non-interventional) natural history control studies.

Thank you for the opportunity to clarify the selection criteria used in the SLR. The purpose of the RWE SLR was to identify studies reporting on clinical effectiveness and safety of existing pharmacological therapies for LHON, with the aim to inform comparative effectiveness and economic analyses of idebenone. Thus, studies presenting anatomical, physiological, genetic, or biochemical or clinical characteristics related to the disease in untreated population or studies that did not make any

reference related to treatment (i.e., it is unclear whether the population was treated or not) were rejected. Moreover, studies presenting outcomes for a population in which only a proportion of patients received treatment (i.e., <80% of patients were treated or untreated) were rejected as the outcomes cannot be fully attributed to the effect of treatment or no active treatment.

In consistency with the SLR inclusion criteria, several studies such as Lam *et al.* (2014)(2), Tonagel *et al.* (2021)(3), Zhao *et al.* (2020)(4), Koenig *et al.* (2019)(5), Mashima *et al.* (2000)(6), and Carelli et al. (2011)(7), which provide outcomes for an intervention and a control group (no active treatment), have been included in the SLR.

In the Company Submission (CS), the PICOS (population, interventions, comparators, outcomes, and study type) category Intervention/Comparator were initially combined in the Inclusion/Exclusion criteria table. In the table below, these have been split and additional description has been added for clarity (Table 1).

Table 1. Revised PICOS framework for RWE SLR

PICOS: RWE SLR	Inclusion	Exclusion
Population	Patients with Leber Hereditary Optic Neuropathy	Disease other than Leber Hereditary Optic Neuropathy
Intervention	No restriction for interventions*	• Studies not reporting outcomes for a treated population • Studies not reporting outcomes representative for standard of care population (i.e., focusing on molecular, anatomic or specific clinical characteristics of the disease) • Non-pharmacological treatments
Comparator	• Any intervention • Best supportive care (including no treatment) • No comparator (single arm)	None
Outcomes	• Efficacy • Safety • QOL/PRO**	Studies not including at least one of the outcomes listed in the Inclusion Criteria
Study Design	Real world evidence studies including: • Prospective observational studies • Retrospective observational studies • Registry analyses • Database analyses	• Non-human/pre-clinical studies • Reviews/Editorials/Notes/Comments/Letters • Case repots/case series

	• Non-interventional studies • Systematic reviews, meta-analyses, indirect comparisons, pooled analysis (for cross-checking)	
Time frame	No limit	None
Language	English studies	Non-English studies
** Studies with a mixed population containing both patients treated with pharmacological therapy (<80%) for LHON and patients not treated for LHON were excluded if the reported outcomes cannot be attributed to a population treated with a specific therapy or to an untreated population* *** QOL/PRO data will be extracted in the QOL/utility data extraction table*		

A5. Please clarify why 108 records were excluded from the real world evidence (RWE) SLR for the exclusion reason "intervention", despite the inclusion criteria stating "No restriction in terms of intervention or comparator"

We reassessed all the 108 reports excluded from RWE SLR to confirm if they met the SLR inclusion criteria. Of 108 reports, 106 reports did not meet the SLR inclusion criteria. A detailed justifications for the inclusion/exclusion of the 108 records has been provided in Appendix 1, Table 31. The exclusion reason for 101 reports remain same as original "intervention" and were excluded due to following reasons:

- Studies reported anatomical, physiological, genetic, or biochemical features of the disease
- Studies did not make any reference to treatment (i.e., it is unclear whether the population was treated or not)
- Studies reported epidemiology of LHON (incidence/ prevalence)

The reason for exclusion was changed for one study to outcomes at is assessed only demographic and genetic characteristics of idebenone-naïve patients with LHON, while one study was excluded as a duplicate (Appendix 1, Table 31). The remaining three studies were excluded on reason "study design": one review and two case series (Appendix 1, Table 31).

Of 108 reports, two reports have been included in the SLR and extracted. The PRISMA has also been revised to reflect the change in exclusion reasons and inclusion of two studies (Appendix 1, Figure 4). Among the two included studies, Yu-Wai-Man, 2021 (REALITY) study, included an overall population of patients with LHON, carrying one of the three primary mutations (m.11778G>A in ND4, m.3460G>A in ND1 and

m.14484T>C in ND6).(8) Among them, 57% of patients had received idebenone. Although the overall population in this study does not meet the inclusion criteria, last-observed mean/median BCVA (LogMAR) in a subgroup of patients ND4 aged ≥15 years at onset treated with idebenone (n=15) has been reported. The data for this subgroup has been extracted. However, this study doesn't provide enough details to be included in an indirect treatment comparison (ITC) analyses as no other details regarding treatment were provided and outcomes were only provided for one subgroup of patients with a specific mutation and are not representative of the overall population under scope.

The second study, Amar, 2015 study is a conference abstract. It reported LogMAR visual acuity, retinal nerve fiber layer (RNFL) thickness, and mean deviation for quinone therapy (it could be either idebenone or EPI-743 - vatiquinone, but this is not clearly stated) among patients with LHON. Due to the very limited data reported in the abstract (average VA reported only), and inability to identify the intervention assessed in the study, the outcomes from this study were not considered.

The updated PRISMA diagram and the table outlining the re-examination of the 108 rejected studies is shown in Appendix 1, Table 31 and Appendix 1, Figure 4.

A6. The EAG notes that studies that are seemingly relevant to the appraisal were excluded at full text review in the RWE SLR due to excluding non-interventional trials, for example the study: "Natural history of patients with Leber hereditary optic neuropathy-results from the REALITY study". However, this is inconsistent with the Company's preferred source of long-term data for patients not treated with idebenone - CaRS I and CaRS II.

a) If the Company agrees that these studies are potentially relevant to the current appraisal, please re-review the trials excluded at the full text stage to ensure no relevant data were missed.

b) Please provide a comparison of the outcomes and risk of bias assessments for the Company's chosen non-interventional studies (CaRS I and CaRS II), and any other relevant studies found when re-appraising.

The scope of the RWE SLR was to identify all observational studies reporting clinical effectiveness and safety of existing therapies for LHON. The REALITY study was re-

examined and now included in the SLR, as it provides some limited data on a subgroup of patients with ND4 mutation aged ≥15 years at onset treated with idebenone.(8) The overall population in REALITY study does not meet the SLR inclusion and cannot be used as a comparator arm for idebenone, as 57% of the patients in this study received idebenone and there are no outcomes available for the untreated subgroup. Moreover, the subgroup data for patients treated with idebenone that is available cannot be used as it is limited to ND4 mutation.(8) Whereas, idebenone is indicated for LHON irrespective of mutation status and thus, subgroup data reported in the REALITY study is not representative for the overall population for this indication. The inclusion of REALITY study would be inconsistent with other studies considered in the economic model.

However, several studies identified in the RWE SLR, such as Lam *et al*. (2014)(2), Tonagel *et al.* (2021)(3), Zhao *et al.* (2020)(4), Koenig *et al.* (2019)(5), Mashima *et al.* (2000)(6), and Carelli et al. (2011)(7), provided outcomes for both an idebenone-treated population and a control group (no active treatment). These studies were reviewed and not included for analysis in the CS. Reasoning is located in Table 2, in response to A7.

A comparison of outcomes between CaRS I and CaRS II is located in Table 10. A quality assessment can be found in Appendix 1, Table 32.

A7. It was unclear how the results of the RWE SLR were considered for inclusion in the Company Submission. Please outline the process by which each included study was considered for the Company Submission.

A total of 36 included publications, reporting data from 22 original studies, were found in the real-world evidence (RWE) systematic literature review (SLR). For the submission, the company considered various factors such as geographical population, gender proportion, study design, intervention type, and sample size for inclusion.

Publications were not included in the Company Submission (CS) if:

- Only abstract was available as not enough details were reported to be included in the CS
- Population was not generalisable to the UK population

- Small sample size
- Intervention is not idebenone.

Due to the factors listed above, the Catarino *et al*. (2020) study emerged as the most robust, being the only multicentre study with UK patients and one of the largest sample sizes.(9) Patients in this study exhibited a mutation distribution similar to the RHODOS trial, encompassing the three primary mutations and comparable gender proportions.(10) Additionally, the Catarino et al. (2020) study has been used to support the long-term economic model of idebenone in other UK HTA submissions including the Scottish Medicines Consortium (SMC), All Wales Medicines Strategy Group (AWMSG), and National Centre for Pharmacoeconomics (NCPE). The table below (Table 2) provides a summary of the 36 included RWE SLR studies.(11–13)

Table 2. Summary of included studies

Short Reference	Publication Type	Country	Source	Study Design	Intervention	Study N (Per arm)	Study N (Overall)	Reasons for exclusion from CS
Catarino_JNO_2020(9)	Original	International	EAP	Retrospective, Multicentre	Idebenone	87	87	-
Metz_ARVO_2014 (abstract)(14)	Update	International (Europe, Australia, New Zealand, USA)	EAP	Prospective, Multicentre	Idebenone	42	42	Abstract
Carlot_ARVO_2020 (abstract)(15)	Subgroup	International	EAP	Prospective, Multicentre	Idebenone	9	9	Abstract
Metz_AO_2015 (abstract)(16)	Update	International	EAP	Prospective, Multicentre	Idebenone	82	82	Abstract
Lloria_EVER_2018 (abstract)(17); Lloria_EVER_2017 (abstract) 2(18)	Update	International	EAP	Retrospective, Multicentre	Idebenone	87	87	Abstract
Lloria_ARVO_2018 (abstract)(19)	Update	International	EAP	Retrospective, Multicentre	Idebenone	87	87	Abstract
Lloria_EVER_2018 (abstract) 2(20)	Update	International	EAP	Retrospective, Multicentre	Idebenone	87	87	Abstract
Lloria_EVER_2017 (abstract)(21)	Subgroup	International	EAP	Retrospective, Multicentre	Idebenone	7	7	Abstract
Klopstock_Neurology_2016 (abstract)(22)	Update	International	EAP	Retrospective, Multicentre	Idebenone	69	69	Abstract
Llòria_EUNOS_2019 (abstract)(23)	Subgroup	International	EAP	Retrospective, Multicentre	Idebenone	40	40	Abstract
Llòria_EUNOS_2019 (abstract) 2(24)	Update	International	EAP	Retrospective, Multicentre	Idebenone	87	87	Abstract
Silva_EUNOS_2019 (abstract)(25)	Subgroup	International	EAP	Retrospective, Chart Analysis	Idebenone	5	5	Abstract
Pemp_EVER_2019 (abstract)(26)	Original	Austria	Department of Ophthalmology, Medical University of Vienna	Prospective, Single Centre	Idebenone	42*	42*	Abstract

Short Reference	Publication Type	Country	Source	Study Design	Intervention	Study N (Per arm)	Study N (Overall)	Reasons for exclusion from CS
Lam_JAMAO_2014(2)	Original	US	Bascom Palmer Eye Institute, University of Miami Miller School of Medicine	Prospective, Single Centre	Idebenone No Idebenone	15 29	44	-Not UK population -Only 1 gene type was assessed (G11778A) -Single centre
Pemp_JCM_2021(27)	Original	Austria	Department of Ophthalmology, Medical University of Vienna	Retrospective, Single Centre	Idebenone	23	23	-Small sample which was divided further into 3 subgroups: Acute, Early chronic and Late chronic -Not UK population -Included other rare mtDNA mutations
Tonagel_GACEO_2021(3)	Original	Germany	Neuro-ophthalmology unit, University Eye Hospital Tuebingen	Retrospective, Single Centre	Idebenone (Cohort 2) Observational (Cohort 1)	7 5	12	-Small sample -Not UK population -Single centre -Included other rare mtDNA mutations and one of the three primary mutations, M14484T>C wasn't detected during the observation period.
Zhao_CER_2020(4)	Original	China	Zhongshan Ophthalmic Centre, Sun Yat-Sen University, Guangzhou	Retrospective, Single Centre, Case-Controlled	Idebenone Control (multivitamin tablets)	20 10	30	-Not UK population -Single centre -Small sample
Pemp_GACEO_2019(28)	Original	Austria	Neuro-Ophthalmology Clinic, Department of	Retrospective, Single Centre	Idebenone	7	7	-Not UK population -Single centre -Small sample

Short Reference	Publication Type	Country	Source	Study Design	Intervention	Study N (Per arm)	Study N (Overall)	Reasons for exclusion from CS
			Ophthalmology and Optometry, Medical University of Vienna					
Zhang_CEO_2019(29)	Original	China	Tongji Hospital of Huazhong University of Science and Technology	Retrospective, Single Centre	rAAV2-ND4	53	53	-Not UK population -Intervention wasn't idebenone
Koenig_ARVO_2019 (abstract)(5)	Original	Germany	University Eye Clinic of Munich	Retrospective, Single Centre	Idebenone	32	32	Abstract
					Observational	31	31	
Catarino_EAN_2019 (abstract)(30)	Original	Germany	Department of Ophthalmology, Ludwig-Maximilian University of Munich	Retrospective, Single Centre	Idebenone	8	8	Abstract
Pemp_ARVO_2018 (abstract)(31)	Original	Austria	Medical University of Vienna	Retrospective, Single Centre	Idebenone	10	10	Abstract
Mashima_JNO_2000(6)	Original	Japan	Keio University Hospital, Tokyo	Retrospective, Single Centre	Idebenone + Riboflavin + Ascorbic acid; then adding Isopropyl unoprostone (since 1994)	14	28	-Not UK population -Small study -Intervention included other non-pharmacological therapy
					Observational	14		
Mejia-Vergara_TVST_2021(32)	Original	US	Doheny Eye Institute of the University of California, Los Angeles	Retrospective, Single Centre	Idebenone	62	62	-Not UK population -Single centre

Short Reference	Publication Type	Country	Source	Study Design	Intervention	Study N (Per arm)	Study N (Overall)	Reasons for exclusion from CS
Orssaud_AO_2012 (abstract)(33)	Original	France	Hôpital Européen Georges-Pompidou HEGP, Paris	Retrospective, Single Centre	Idebenone + Vitamin B2 + Vitamin C	75	75	Abstract
Carelli_Brain_2011(7)	Original	Italy	University of Bologna	Retrospective, Single Centre	Idebenone	44	103	-Not UK population -Single centre
					Observation	59		
Jancic_EN_2011 (abstract)(34)	Original	Serbia	School of Medicine University of Belgrade, Clinic of Neurology and Psychiatry for Children and Youth, Belgrade	Retrospective, Single Centre	Idebenone	9	9	Abstract
Orssaud_INOS_2012 (abstract)(35)	Original	France	NR	Retrospective, NR	Idebenone	80	80	Abstract
Borrelli_AJO_2022(36)	Original	Italy	San Raffaele Scientific institute	Retrospective, Single Centre	Idebenone	17	17	-Not UK population -Small sample -Single centre
Stephenson_NO_2022(37)	Original	Ireland	Neuro-Ophthalmology department of the Royal Victoria Eye & Ear Hospital, Dublin, Ireland	Retrospective, Single Centre	Idebenone	22	44	-Single centre -included other rare mutation
Gopalakrishnan_IJO_2023(38)	Original	India	Tertiary eye care institute in India	Retrospective, Single Centre	Low Vision Devices (LVDs)	74	74	-Not UK population -Single centre
Van Everdingen_AO_2022 (39); Van	Original	Netherlands	Three Dutch hospitals	Retrospective, Multicentre	Idebenone	72	72	-Not UK population

Short Reference	Publication Type	Country	Source	Study Design	Intervention	Study N (Per arm)	Study N (Overall)	Reasons for exclusion from CS
Everdingen_AO_2022 (abstract)(40); Pott_EUNOS_2022(41)								
Bhate_JPOS_2022(42)	Original	India	Children's Eye Care Centre, L. V. Prasad Eye Institute	Retrospective, Single Centre	Idebenone	55	55	-Not UK population -Single centre

Abbreviations: CS – Company submission; EAP – Expanded Access Program; mtDNA – Mitochondrial deoxyribonucleic acid; USA – United States of America; UK – United Kingdom

Analysis Sets

A8. Priority question. The EAG notes that there are numerous analysis populations reported throughout the submission for each study. Please complete the following table of the various analysis populations available for each study, providing justification for whether or not they were included in the economic modelling.

The main studies used to inform the CEA were: RHODOS (idebenone and SoC arms between baseline and 6 months), EAP (idebenone arm 6 months to 36+ months) and the CaRS (SoC arm 6 months to 36+ months).

The RHODOS study is considered the basis of the CEA, as this is a randomised, double-blind, placebo-controlled, multicentre trial and the first to assess the clinical effectiveness of idebenone for the treatment of LHON. As the EAP study has a similar mutation distribution to RHODOS, and the longest trial duration of any idebenone studies, this is the preferred long term data source.

The analysis populations for the RHODOS, EAP, LEROS, CaRS I and CaRS II can be found in Table 3.

Table 3. Analysis populations across clinical evidence package

Study	RHODOS			LEROS			EAP		CRS-I			CRS-II		
Analysis set	OFU	ITT	mITT	mITT/ITT ≤1 year after onset of symptoms	mITT/ITT >1 year after onset of symptoms	NH comparator group (reported as N=587 in Table 10)	LHON Population	Efficacy Population	CRFs received (unique, date of onset known)	Natural history population	Natural history outcomes population	CRFs received (unique, date of onset known)	Natural history population	Natural history outcomes population
N	58	82	81	ITT: 109 mITT: 99	ITT: 87 mITT: 82	N= 587 NH matched comparator: 106	105	87	383	106	74	N/A	219	

Informs Company base case	No	Yes	No	No			No	Yes	No	No	Yes	No
Description	60 patients (Previous treatment in RHODOS: idebenone: 41 patients; placebo: 19 patients) of whom 58 provided VA data.	Out of the 85 patients randomised, three patients were prospectively excluded from the ITT population for all VA analyses due to inaccurate recordings in VA measurements either at baseline or at Visit 5	The mITT population was same as the ITT, but for VA and colour contrast analyses, one patient (randomised to placebo) who was identified as a natural history confounder due to ongoing spontaneous recovery of vision at the time of randomisation into the study population was excluded	Patients with symptoms onset in the most recent eye (second eye) ≤1 year at Baseline	Patients with symptoms onset in the most recent eye (second eye) >1 year at Baseline	The NH data set consisted of 106 patients who contributed 193 eyes for the evaluation.	Patients who had post-Baseline VA efficacy data available	Patients who carried one of the 3 major LHON-causative mtDNA mutations, who had time since onset at Baseline of less than 12 months in the most recently affected eye and for whom post-Baseline VA efficacy data was available	CRFs with the following characteristics were excluded: Reported idebenone use (n= 188) Participation in RHODOS or the EAP (n=3) LHON not associated with the G11778A, G3460A or T14484C mtDNA mutations (n=21) Unknown date of onset of symptoms (n=44)	Patients for whom the progression of VA change with time could be assessed in order to address the secondary endpoints	Patients for who the results of a post-Presentation VA assessment in the ≥3-24 month window required for comparison with the EAP outcomes were available	All enrolled patients who had provided a patient data release agreement to participate in the study, as required by local regulations.
Rationale for including/not including in economic model	RHODOS-OFU looks only at VA following discontinuation from idebenone,	As RHODOS is a randomised, double-blind, placebo-controlled, multicentre trial and the first to assess the clinical effectiveness of idebenone for the treatment of LHON, the data collected within this study was considered as the basis of this CEA		The company considers the EAP to be the best source of long-term effectiveness in the model because the EAP study has longer follow-up data, spanning 36 months compared to the LEROS trial, which was 24 months. For more details, please see Section B.3.3.2 in CS			The company considers the EAP to be the best source of long-term effectiveness in the model because the EAP study has longer follow-up data, spanning 36 months compared to the LEROS trial, which was 24 months. For more details, please see Section B.3.3.2 in CS		The CRS-I study demonstrates the disease course of LHON in patients who only received SoC			This study was designed specifically to inform the natural history control group of the LEROS study. The endpoints in this study don't align with what was captured in RHODOS.

Abbreviations: CRFs – case report forms; CS – Company submission; EAP – Expanded Access Program; ITT – intent-to-treat; mITT – modfied intent-to-treat; mtDNA – Mitochondrial deoxyribonucleic acid; N/A – no answer; NH – natural history; SoC – standard of care; VA – Visual acuity

A9. The EAG notes that the modified intent-to-treat (mITT) population was the population used for the efficacy analysis of the RHODOS trial reported in the company submission (CS). Please provide any further information available about the patient in the placebo group excluded from the mITT analysis due to ongoing spontaneous recovery of vision, and please provide a comparison of the following primary and secondary trial endpoints for the ITT vs mITT population:

- Best recovery of logMAR visual acuity in either right or left eye;
- Change in best visual acuity;
- CRR.

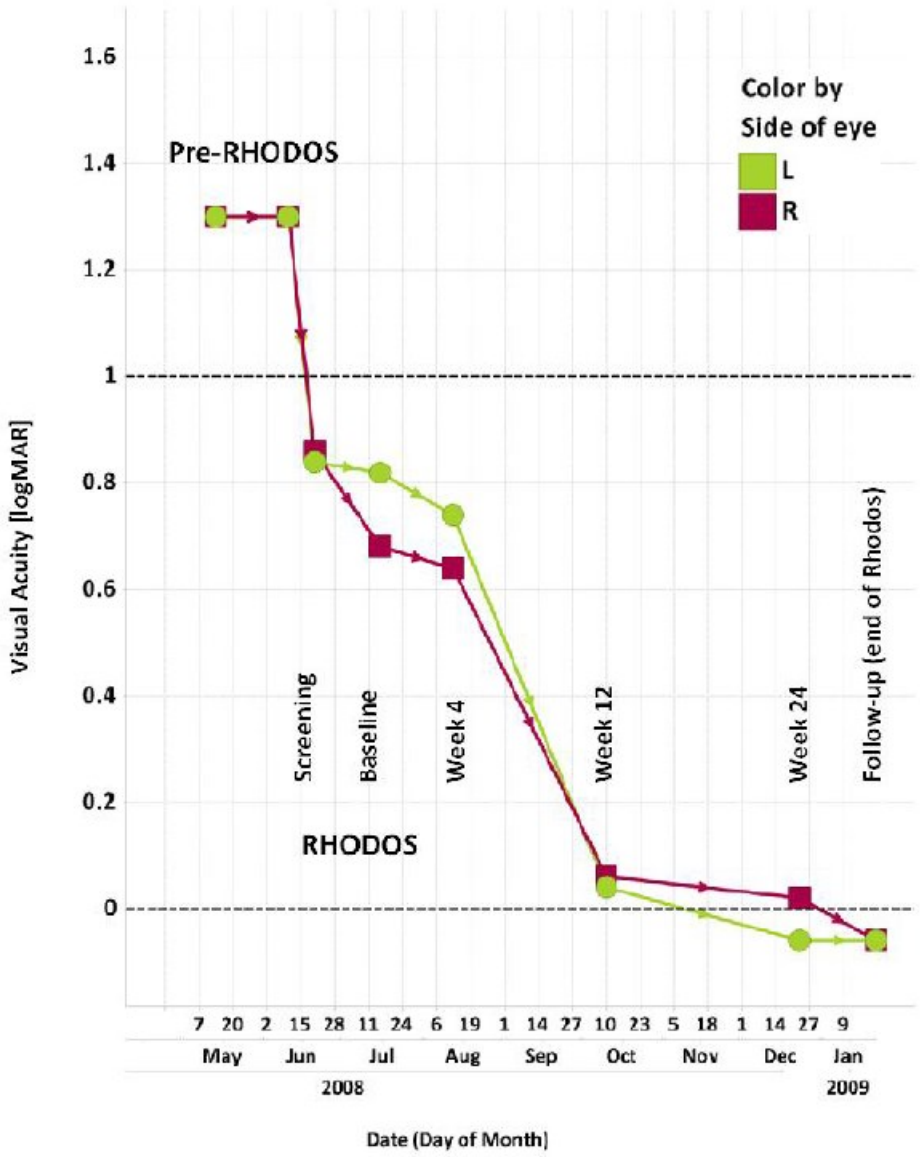
Identification of Patient 23 as natural history confounder

The mITT population was the same as the ITT population except for the VA and colour contrast analyses which excluded Patient 23 (randomised to placebo). Patient 23 was identified as a natural history confounder due to on-going spontaneous recovery of vision at the time of randomisation into the study.(1) Below are details of how patient 23 was identified as natural history confounder:

By comparing the trajectories of historical VA changes for each patient enrolled in RHODOS it became clear that whilst patients generally had already lost vision in one or both eyes prior to enrolment into RHODOS, the trajectory of VA change for Patient 23 just prior to enrolment into RHODOS and within one year of onset of symptoms showed a completely different picture.

The earliest VA data available for Patient 23 (from May/June 2008) documented severe bilateral vision loss (logMAR >1.0 in both eyes, i.e. the patient was legally blind). The worst reported VA (logMAR 1.3 in both eyes) was measured on June 10, 2008, but 10 days later, on the occasion of the screening visit for the RHODOS study, the patient's VA had already improved by approximately 5 lines (left eye: logMAR 0.84; right eye: logMAR 0.86) with further bilateral improvement between the Screening and Baseline visits as seen in Figure 1.

Figure 1. Trajectory of VA changes for Patient 23 prior to and during RHODOS



Source: Addendum to the Statistical Analysis Plan for RHODOS. (43)

Patient 23 developed vision loss following surgery for appendectomy complicated by peritonitis probably under the influence of the anaesthetics used. He was later diagnosed with the G11778A mtDNA mutation. The close temporal relation between the exposure to anaesthetics and vision loss in this patient is of special interest, as it has been described that exposure to environmental factors (including anaesthetics and other chemical agents) can precipitate symptom onset in LHON mutation carriers with previously unaffected vision. Furthermore, it is possible that patients may recover from such chemical insult and regain vision, despite the G11778A mtDNA mutation,

which normally results in a more severe disease with very limited probability for spontaneous vision recovery.

Due to this unusual trajectory of VA with marked improvement immediately prior to enrolment into RHODOS, Patient 23 clearly represents a non-typical medical case and a clear exception within the study population and Patient 23 has to be considered as outlier and possible confounder on medical grounds to the outcome of the VA endpoints of the study.

Therefore, in agreement with recommendations (Section 5.3 of ICH E9 Notes for Guidance on Statistical Principles for Clinical Trials)(44) to be followed when confounders are identified, it is medically justified to exclude such patients from the analysis. Accordingly, Patient 23 was excluded from all VA analyses in a newly defined mITT population.

Comparison of ITT vs mITT

As requested, comparisons of the following primary and secondary trial endpoints for the ITT vs mITT population are provided below:

Best recovery of logMAR VA in either right or left eye

Results for both the ITT and mITT populations for best recovery of logMAR VA in either right or left eye are summarised in Table 4.(1)

Table 4. Best recovery in VA (ITT and mITT population)

	Estimated Change (95% CI) [estimated change in letters]		Estimated Difference ± SEM (95% CI) [estimated change in letters]	p-value
	Idebenone	Placebo		
ITT population				
N	53	29		
Week 24	−0.135 (−0.216, −0.054) [+6 letters]	−0.071 (−0.176, 0.034) [+3 letters]	−0.064 ± 0.061 (−0.184, 0.055) [3 letters]	0.291
mITT population				
N	53	28		

	Estimated Change (95% CI) [estimated change in letters]		Estimated Difference ± SEM (95% CI) [estimated change in letters]	p-value
	Idebenone	Placebo		
Week 24	−0.136 (−0.212, −0.060) [+6 letters]	−0.036 (−0.137, −0.065) [+1 letter]	−0.100 ± 0.058 (−0.214, −0.014) [5 letters]	0.0862

Abbreviations: CI – Confidence interval; ITT – Intent-to-treat; mITT – Modified intent-to-treat; SEM – Standard error of the mean.

Change in best visual acuity

Results for both the ITT and mITT populations for change in best visual acuity are summarised in Table 5.(1)

Table 5. Change in best VA (ITT and mITT population)

	Estimated Change (95% CI) [estimated change in letters]		Estimated Difference ± SEM (95% CI) [estimated change in letters]	p-value
	Idebenone	Placebo		
ITT population				
N	53	29		
Week 24	−0.035 (−0.216, −0.055) [+1 letter]	0.085 (−0.032, 0.203) [−4 letters]	−0.120 ± 0.068 (−0.2546, 0.0137) [6 letters]	0.078
mITT population				
N	53	28		
Week 24	−0.037 (−0.123, −0.049) [+1 letter]	0.123 (0.010, 0.237) [−6 letters]	−0.160 ± 0.065 (−0.289, −0.031) [8 letters]	0.015

Abbreviations: CI – Confidence interval; ITT – Intent-to-treat; mITT – Modified intent-to-treat; SEM – Standard error of the mean

CRR

CRR was assessed only in the mITT population, and therefore a comparison cannot be presented.

A10. The RHODOS CSR states that: [redacted] Please detail how it was decided that these patients had inaccurate readings, and please outline whether these patients had valid Visit 2, 3, or 4

measurements that the inaccurate Baseline or Visit 5 measurements could have been imputed from. If so, please provide a sensitivity ITT analysis using these data.

[redacted]

This is justified as discrepancies in the visual acuity tests at Baseline and Visit 5 will affect the primary and secondary endpoints using visual acuity (measured in logMAR) as the efficacy variable. Below are details of how it was decided that these patients had inaccurate readings:

Patient 5

Visual acuity was measured at 1 meter (m) distance in the right eye and Counting Fingers in the left eye at Screening, then at 1m distance in both eyes at Visit 2 (Baseline), Visit 3, Visit 4 and Visit 6. However, visual acuity is measured only at 4m distance at Visit 5, without the per protocol progression to a 1m distance reading despite having <20 letters read at 4m distance. This would appear to indicate a large improvement in visual acuity. However, there is strong evidence to doubt the accuracy of this data. First, the Visit 5 data point is not consistent with all of the other data points for this patient as described above. Second, the indication of improvement in the patient's visual acuity is not consistent with information yielded by the patient's self-reported VF-14 test which does not show any improvement. These facts suggest that for Visit 5 the examiner may have mistakenly transcribed the patient's visual acuity score in the 4m distance rows rather than the 1m distance rows. Therefore, it is recommended that both eyes of this patient are to be excluded from the primary analysis of all study endpoints analysing log MAR-based visual acuity data.

Patient 13

Visual acuity was measured at 1m distance in both eyes at Screening, Visit 2 (Baseline), Visit 3, and Visit 4 but measured only at 4m distance at Visit 5 and Visit 6. Based on the significant difference from and inconsistency with all prior visual acuity scores, it cannot be excluded that this apparent improvement observed at Visit 5 and

Visit 6 is due to a documentation error. Therefore, it is recommended that both eyes of this patient are to be excluded from the primary analysis of all study endpoints analysing logMAR-based visual acuity data.

Patient 20

In both eyes at Visit 2 (Baseline), visual acuity was correctly measured at 1m distance as per protocol after a failure to read ≥ 20 letters at 4m distance. At Visit 5, the examiner did not progress to evaluation at 1m distance after failure to read ≥ 20 letters at 4m distance and therefore the evaluations are inconsistent with each other, thereby introducing a potential bias and source of error. Therefore, it is recommended that both eyes of this patient are to be excluded from the primary analysis of all study endpoints analysing log MAR-based visual acuity data.

A sensitivity analysis was performed for the whole ITT population including data from the 3 randomised patients who were excluded from the ITT population. Results are presented in Table 6 below.

Table 6. Primary efficacy endpoint: Best recovery of logMAR visual acuity for total all randomised patients, including patients excluded from ITT

Change baseline to	Estimated change* (95% CI)		Estimated Difference ± SEM (95% CI)	p-value
N	Idebenone	Placebo	Idebenone vs Placebo	
Week 4	-0.0760 (-0.1560, 0.0040)	-0.0267 (-0.1287,0.0752)	-0.0493 (-0.1660, 0.0675)	0.4060
Week 12	-0.0785 (-0.1594, 0.0024)	-0.0347 (-0.1366,0.0673)	-0.0438 (-0.1613, 0.0737)	0.4624
Week 24	-0.1468 (-0.2279, -0.0658)	-0.0890 (-0.1935, 0.0154)	-0.0578 (-0.1769, 0.0612)	0.3388
Week 4-24[Ŧ]	-0.1004 (-0.1724, -0.0284)	-0.0501 (-0.1398, 0.0395)	-0.0503 (-0.1502, 0.0496)	0.3191

*Data is estimated mean from mixed model for repeat measures (MRRM)
[Ŧ]Estimated mean change from baseline to average of weeks 4, 12 and 24 using MMRM
Abbreviations: CI – Confidence interval; SEM – Standard error of the mean

Patient characteristics

A11. Priority question. The baseline characteristics reported across studies included in the CS differ, making it difficult to assess the similarity of the

patient populations across the studies used in the CS. Please complete the following table of baseline characteristics for each study.

The Company have completed the table below (Table 7) as per the EAG's request. Note where a characteristic has not been captured in the trial, we have recorded NR (not reported).

Table 7. Baseline characteristics across studies

	RHODOS		EAP		LEROS		CaRS I		CaRS II	
Characteristic	Idebenone N=55 (N=53 ITT population)	Placebo N=30 (N=29 ITT population)	LHON population N=105	Efficacy population N=87	ITT N=196	NH matched comparator N=106	Natural history population N=106	Natural history outcomes population N=74	Natural history population N=219	Natural history outcomes population N=219
Age, mean ± SD [median] (range) (years)	33.8 ± 14.8 [30.0] (14–63)	33.6 ± 14.6 [28.5] (14–66)	31.7±18.5 [23.6] (6.9–80.1)	31.9±17.4 [24.6] (6.9–80.1)	34.1 ± 15.2 [31.9] (12.1–79.2)	32.1 ± 14.5 [28.0] (13.0–75.0)	32.4 (15.5) [29.5] (6 – 79)	31.1 ± 14.6 (7 – 75)	30.0±15.0 [26.0] (6-68)	30.0±15.0 [26.0] (6-68)
Male, n (%)	47 (85.5)	26 (86.7)	82 (78.1%)	71 (81.6%)	144 (73.5)	88 (83.0)	85 (80.2)	61 (82.4)	175 (79.9)	175 (79.9)
Age at symptom onset mean ± SD [median] (range) (years)	NR	NR	30.8±18.5 [23.0] (6.6 - 78.9)	31.4±17.3 [24.2] (6.6 - 78.9)	32.5 ± 15.2 [30.4] (8.8 – 78.2)	31.7 ± 14.5 [28] (13.0 – 75.0)	32.1 ± 15.4 [29.5] (6 – 78)	30.9 ± 14.6 (7 – 75)	29.8±15.0 [26.0] (6-68)	29.8±15.0 [26.0] (6-68)
Age at diagnosis mean ± SD [median]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Race, n (%)										
Caucasian/white	53 (96.4)	30 (100)	NR	NR	54 (27.6)	NR	NR	NR	NR	NR
Black	1 (1.8)	0	NR	NR	8 (4.1)	NR	NR	NR	NR	NR
Other	1 (1.8)	0	NR	NR	134 (68.4)	NR	NR	NR	NR	NR
Mutations, n (%)										

	RHODOS		EAP		LEROS		CaRS I		CaRS II	
G11778A	37 (67.3)	20 (66.7)	61 (58.1)	54 (62.1)	112 (57.1)	77 (72.6)	78 (73.6)	55 (74.3)	157 (71.7)	157 (71.7)
T14484C	11 (20.0)	6 (20.0)	17 (16.2)	16 (18.4)	34 (17.3)	12 (11.3)	11 (10.4)	7 (9.5)	32 (14.6)	32 (14.6)
G3460A	7 (12.7)	4 (13.3)	18 (17.1)	17 (19.5)	35 (17.9)	17 (16.0)	17 (16.0)	12 (16.2)	30 (13.7)	30 (13.7)
Other	-	-	2 (1.9)	-	5 (2.6)	-	-	-	-	-
Negative	-	-	-	-	10 (5.1)	-	-	-	-	-
Months since onset of vision loss, mean ± SD [median] (range)	22.8 ± 16.2 [17.8] (3–62)	23.7 ± 16.4 [19.2] (2–57)	10.6±18.7 [5.6] (0.9 - 133.7)	6.2±3.7 [5.0] (0.9 - 16.7)	18.4±15.8 [12.3] (0.3-58.3)	NR	Years: 0.3±0.4 [0.2] (0.0– 1.9)	Years: 0.3±0.4 [0.1] (0.0– 1.9)	3.4±5.6 [1.7] (0.7-3.9)	3.4±5.6 [1.7] (0.7-3.9)
Proportion of patients with nadir prior to baselines, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Months since nadir at baseline, mean ± SD [median] (range)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Patients with onset of symptoms >1 year, n (%)	36 (65.5)	19 (63.3)	NR	NR	87 (44.4)	NR	8 (7.5)	2 (2.7)	10 (4.6	10 (4.6)
Onset of vision loss within 1 year, n (%)	19 (34.5)	11 (36.7)	NR	NR	109 (55.6)	NR	98 (92.5)	72 (97.3)	209 (95.4)	209 (95.4)
Baseline logMAR distribution, n (%)										
One eye logMAR ≥1.0	5 (9.4)	2 (6.9)	Best VA: 70 (66.7)	Best VA: 63 (72.4)	NR	NR	NR	NR	NR	NR

	RHODOS		EAP		LEROS		CaRS I		CaRS II	
Both eyes logMAR ≥1.0 (legally blind)	45 (84.9)	25 (86.2)	NR	NR	NR	NR	50 (47.1)	27 (36.5)	82 (37.7)	82 (37.7)
Both eyes logMAR <1.0	3 (5.7)	2 (6.9)	NR	NR	NR	NR	NR	NR	NR	NR
One eye off-chart	11 (20.8)	3 (10.3)	Best VA: 18 (17.1)	Best VA: 17 (19.5)	NR	NR	NR	NR	NR	NR
Both eyes off-chart	25 (47.2)	13 (44.8)	NR	NR	NR	NR	12 (11.3)	7 (9.5)	19 (8.8)	19 (8.8)
Both eyes on-chart	17 (32.1)	13 (44.8)	NR	NR	NR	NR	NR	NR	NR	NR
Patients with both eyes off-chart,* n (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Patients with discordant visual acuities,† n (%)	20 (37.7)	10 (34.5)	NR	NR	NR	NR	NR	NR	NR	NR
LogMAR: mean ± SD,‡ (n)										
Best eye	1.61 ± 0.64 (53)	1.57 ± 0.61 (29)	1.16 ± 0.55	1.23 ± 0.52	1.15 ± 0.60	NR	0.75 ± 0.61	0.62 ± 0.61	0.94 ± 0.64 (438)	0.94 ± 0.64 (438)
Worst eye	1.89 ± 0.49 (53)	1.79 ± 0.44 (29)	NR	NR	NR	NR	NR	NR	NR	NR
Both eyes	1.75 ± 0.58 (106)	1.68 ± 0.54 (58)	NR	NR	1.26 ± 0.55	NR	1.03 ± 0.60	0.97 ± 0.63	NR	NR

*Off-chart defined as >logMAR 1.68 (patients unable to read any letter on the chart).
†Defined as patients with difference in logMAR>0.2 between both eyes

‡Applying logMAR 2.0 for counting fingers; logMAR 2.3 for hand motion; logMAR 2.6 for light perception
Abbreviations: NR – Not Reported; SD – Standard deviation

A12. Please clarify how nadir was identified and defined for each patient across the RHODOS, LEROS, the EAP and CaRS Studies. Please indicate if the definition of nadir was different between any of these studies, and clarify if nadir was identified by the patient, by eye, or by both patient and eye.

In RHODOS, the nadir was not formally assigned as this was not a commonly understood concept at the time. Similarly in the natural history, as this was not being actively looked for, it is very difficult to retrospectively assign the time to nadir and often also accurately the depth of the nadir in terms of visual acuity as this requires frequent VA assessments. The definition however is the same in all studies, the point of worst visual acuity.

A13. The EAG notes that there was meaningful heterogeneity between studies in terms of visual acuity at baseline, which may be related to prognosis. As summary statistics may not adequately describe patients baseline VA, especially considering the mixture of off-chart and on-chart patients, please provide an equivalent of Figure 12 from the RHODOS CSR (Visual Acuity at Baseline [ITT population]) for:

- LEROS ITT population;
- EAP LP population;
- CaRS I;
- CaRS II.

A response to A13 will be shared on 12th December.

A14. As mtDNA mutation is a key prognostic factor for people with LHON, please can the company:

- Provide an evidence-based estimation of the current prevalence of mtDNA genotypes within the UK LHON population;
- Complete the following table detailing the size of the UK subgroups and genotype prevalences across the idebenone clinical trial and natural history study populations. Please outline if patients could contribute data to each source, i.e., be counted twice, and, if they could, please outline how many did.

Table 8: mtDNA prevalence rates

Study	**N**	G11778A N (%)	T14484C N (%)	G3460A N (%)	Other N (%)	Negative N (%)	**N UK**	G11778A UK subgroup	T14484C UK subgroup	G3460A UK subgroup	Other UK subgroup	Negative UK subgroup
RHODOS	**85**	57 (67.1)	17 (20.0)	11 (12.9)	-	-	**30**	Not Detailed	Not Detailed	Not Detailed	Not Detailed	Not Detailed
EAP	**111**	63 (56.8)	17 (15.3)	18 (16.2)	11 (10.8)	2 (1.8)	11	8 (72%)	0 (0)	1 (9%)	2 (18%)	Not Detailed
LEROS	**198**	112 (56.6)	34 (17.2)	35 (17.7)	5 (2.5)	12 (6.1)	**29**	Not Detailed	Not Detailed	Not Detailed	Not Detailed	Not Detailed
PAROS	**224**	117 (52.22)	40 (17.9)	32 (14.3)	27 (12.1)	-						
CRS I	**106**	78 (73.6)	11 (10.4)	17 (16.0)	-	-						
CRS II	**217**	157 (71.7)	32 (14.6)	30 (13.7)	-	-	**20**	Not detailed	Not detailed	Not detailed	-	-

Note – the mutation status of 8 (3.6%) of CRS I patients was unknown at baseline.
Note: No UK patients participated in CRS 1.
Note: In CRS 1 No studied patients contributed to RHODOS or EAP

Yu-Wai-Man et al 2003 and Gorman et al 2015 are the only UK specific papers that have looked at split by genotype.(45,46) Yu-Wai-Man et al describes the relative frequency of each primary LHON mutation as follows: G11778A, 60% (9 of 15 genetically independent maternal pedigrees); G3460A, 33% (5 pedigrees); and T14484C, 7% (1 pedigree).(46) Gorman et al 2015 was a follow up study to Man et al which found the following rates: G11778A, 55%, G3460A, 37% and T14484C, 8%.(45) In both these studies G3460A has a higher prevalence than other European studies and caution should be taken in extrapolating to the whole of England.

In Table 8 above, CRS1 mentions 383 patients, but only 106 are considered in Natural History cohort. The reasons were:

- Patients with the following characteristics were excluded:
    - Reported idebenone use (n= 188)
    - Participation in RHODOS or the EAP (n=3)
    - LHON not associated with the G11778A, G3460A or T14484C mtDNA mutations (n=21)
    - Unknown date of onset of symptoms (n=44)

These criteria reduced to 137 the number of CRFs available for inclusion in the Natural History dataset. Upon analysis it was noted that for 31 of these CRFs, the first reported VA assessment were made >2 to 49.6 years after Onset, i.e. beyond the timeframe within which LHON-associated VA changes might be expected. Furthermore, in 25 of these, only a single VA assessment was available, rendering the data extremely sparse and not reliably representative of the natural history of LHON. These CRFs were therefore excluded, reducing to 106 the total number of patients for inclusion in the Natural History Population. For CRS-2, the total number of patients included was 219. Of these, 10 were already included in the previous CRS. For those, all VA assessments were included in the analysis. Of the 219 patients, 217 had at least one VA assessment post-Baseline.

Study design and patient disposition

A15. Please clarify at which time patients were unblinded in RHODOS prior to the observational follow-up.

Patients were unblinded at the end of Week 24 in the RHODOS trial. The median time that had elapsed between Week 24 of RHODOS and the RHODOS-OFU was 30 months (range: 20.9 to 42.5 months; 131 weeks). During the RHODOS-OFU study period, patients were not treated with idebenone.

A16. Please clarify why Figure 17 of the CS and Figure 1 in the CSR of the EAP appear to have contrasting numbers of patient data available on treatment at each time point.

Month	0	6	12	24	36	48
Patients left in treatment (CS Figure 17, EP)	87	65	42	19	7	4
Months	>0	>6	>12	>24	>36	>42
Patients with treatment duration, CSR, Figure 1, EP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 17 of the CS details the proportion of patients at each time point that experience a clinically relevant response (CRR), not the proportion who remain on treatment (as presented in Figure 1 of the EAP CSR).

A17. The EAG has created the following table showing the amount of patient data available from the EAP and LEROS over time. Please can the Company verify whether these data are accurate and if they have a similar interpretation?

Months	>0	>6	>12	>24
EAP: Patients with treatment duration, CSR, Figure 1, EP, N (%)	87 (100%)	81 (93.1%)	63 (72.4%)	42 (48.3%)
Months	1 day	>6	>12	>24

Duration of follow-up, LEROS safety population, N (%)	[redacted]	[redacted]	[redacted]	[redacted]

The company can verify that data are accurate for both the EAP and LEROS trial. The efficacy population in the EAP contains only patients who carried one of the three major LHON-causative mtDNA mutations, who had time since onset at baseline of less than 12 months in the most recently affected eye and for whom post-baseline VA efficacy data was available. The LEROS safety population includes patients with mutations outside of three major mtDNA mutations. Additionally, the LEROS duration of follow up does not necessarily describe the number of patients who have data available and therefore the two datasets are not comparable.

For interpretation of availability of data, please refer to Table 9 in response to Question A18.

A18. Based on the table outlined in question A17 please provide a similar table including the amount of data available at each timepoint from each of the key analysis sets, including but not necessarily limited to: RHODOS, EAP, LEROS, CaRS I, CaRS II and PAROS.

Table 9 details the level of data available from the key submission studies.

Table 9. Data availability across trials

Months	>0	>6	>12	>24
RHODOS ITT: Patients with outcome data available N (%)	Week 4: 81 (98.8%)	Week 24: 76 (92.7%)	-	-
Idebenone	53	50	-	-
SoC	29	26	-	-
EAP EP: Patients with outcome data available N (%)	87 (100.0%)	81 (93.1%)	63 (72.4%)	42 (48.3%)
LEROS ITT: Patients with outcome data available N (%)	196 (100.0%)	171 (87.2%)	151 (77.0%)	125 (63.7%)

LEROS matched comparator population: Patients with outcome data available N (%)	-	194 (100%)	-	93 (47.9%)
CaRS I Natural history population: Patients with outcome data available N (%)	106 (100%)	-	-	-
CaRS I Natural history outcomes population: Patients with outcome data available N (%)	74 (100%)	-	-	-
CaRS II Natural history population: Patients with outcome data available N (%)	219 (100%)	203 (92.7%)	58 (26.5%)	26 (11.9%)
PAROS safety population: Patients with outcome data available N (%)	224 (100.0%)	208 (92.9%)	186 (83.0%)	107 (47.8%)

Abbreviations: EP – Efficacy population; ITT – Intent-to-treat; SoC – Standard of care

Analyses

A19. The EAG notes the choice of logMAR values assigned to the semi-quantitative ('off-chart') visual acuity steps of counting fingers (logMAR 2.0), hand motion (logMAR 2.3) and light perception (logMAR 2.6) were based on Lange *et al.* 2009 (referred to in RHODOS CSR). Please provide the reference Lange *et al.* 2009.

The company have supplied the reference alongside response document.

A20. Priority question. In Appendix M it is noted that for LEROS, "the natural history control set consisted of data obtained from the case record survey (CaRS) and CaRS II studies". However, it is also stated that "Results from the CaRS II study are not yet available". The EAG notes that the size of the Natural History comparator group (CRS-1 and CRS-2 combined), is large, with N=587 at Day 1 and N=372 considered eligible for matching to LEROS. Please:

a) Clarify how data from the CaRS II study were able to inform the LEROS analysis if the results of CaRS II are not yet available.

b) Provide a breakdown of the number of patients from CaRS I and CaRS II that make up the NH-matched comparator cohort in LEROS.

c) Provide a full written summary of the results of CaRS II, and also provide any study protocol, SAPs and CSRs that are currently available.

A response to A20 will be shared on 12th December.

A21. Priority question. The EAG notes that outcome data across RHODOS, EAP, LEROS and CaRS are not aligned. Please provide outcome data for the outcomes of: change in best VA, best recovery of logMAR visual acuity in either right or left eye, clinical relevant recovery (CRR) that is comparable to that provided for the RHODOS trial for LEROS, EAP and CaRS natural history cohorts. Please provide outcome data reflecting both change from baseline and change from nadir for the populations specified in the table below.

Table 10 contains the outcome data split by clinical trial. Where an outcome was not captured in a trial, we have marked “not an outcome measure”. Where data is only reported for one trial population, we have marked “NR” (not reported) against the other population.

Table 10. Outcome data by trial

Outcome		RHODOS(1)		EAP(9)		LEROS(47)		CaRS I(48)		CaRS II(49)	
		Idebenone	Placebo	LHON population	Efficacy population	ITT	NH matched comparator	Natural history population	Natural history outcomes population	Natural history population	Natural history outcomes population
	N	53	29	105	87	196	106	106	74	219	219
Change in best VA (from baseline)	Final analysis time-point	Week 24: -0.035 (-0.126, 0.055) [+1 letter]	Week 24: 0.085 (-0.032, 0.203) [-4 letters]	Best logMAR at baseline 1.16±0.55 (1.30) [-0.18, 1.80] Best logMAR at last visit 1.09±0.66 (1.28) [-0.18, 1.80]	Best logMAR at baseline 1.23±0.52 (1.36) [-0.18, 1.80] Best logMAR at last visit 1.19±0.63 (1.38) [-0.16, 1.80]	Month 24: Mean (SD) [min,max] N= 70 2nd eye onset ≤1 year: -0.09 (0.72) [-1.78, 1.84] N=55 2nd eye onset >1 year: --0.19 (0.31) [-1.24, 0.12]	NR	NR	Mean (SD): 0.97 (0.63) Median (range): 1.09 (-0.11 – 1.7)	NR	1st year follow up: 0.53±0.63 (0.40) [-0.90, 2.00] 5th year follow up: 0.23±0.95 (0.10) [-1.40, 2.00]
Change in best VA (from nadir)	Final analysis time-point	Not an outcome measure	Not an outcome measure	-0.70±0.44 (-0.60) [-1.80, -0.20]	-0.72±0.46 (-0.62) [-1.80, -0.20	Not an outcome measure	Not an outcome measure	NR	Mean (SD): 1.60 Median (range): 1.70 (-0.52 – 1.7)	Not an outcome measure	Not an outcome measure
Best recovery of logMAR visual		Week 24: -0.135 (-0.216, -	Week 24: -0.071 (-0.176,	Not an outcome measure	Not an outcome measure	Not an outcome measure	Not an outcome measure	Not an outcome measure	Not an outcome measure	Not an outcome measure	Not an outcome measure

acuity in either right or left eye (from baseline)		0.054)[+6 letters]	0.034) [+3 letters]								
Best recovery of logMAR visual acuity in either right or left eye (from nadir)		Not an outcome measure	Not an outcome measure	Not an outcome measure	Not an outcome measure	Not an outcome measure	Not an outcome measure	Not an outcome measure	Not an outcome measure	Not an outcome measure	Not an outcome measure
CRR (from baseline)	Final analysis time-point	Not an outcome measure	Not an outcome measure	Patients: 42 (40.00%)	Patients: 31 (35.63%)	Eye onset ≤ 1 year: N=44 (40.4%) Eye onset>1 year N=33 (32.4%)	NR	Not an outcome measure	Not an outcome measure	NR	CRR from baseline at 12 months in eyes ≤1 year onset: N(all eyes)=96 Mean (SD): 32.1 (15.3) Median:30 (17.5-42) CRR from baseline at 12 months in eyes > 1 year onset: N(all eyes)=11 Mean (SD): NA Median: NA
CRR (from nadir)	Final analysis time-point	Not an outcome measure	Not an outcome measure	53 (50.5%)	40 (46.0%)	Eye onset ≤ 1 year:	NR	NR	Patients: 24 (50%)	Not an outcome measure	Not an outcome measure

						N=53 (48.6%) Eye onset >1 years: N=37 (36.3%)			Eyes: 38 (39.6%)		

Abbreviations: CRR – Clinically relevant recovery; ITT – Intent-to-treat; logMAR – Logarithm of the minimum angle of resolution; NA – Not available; NH – Natural history; NR – Not reported; SD – Standard deviation; VA – Visual acuity

A22. The main secondary outcome in the RHODOS trial: change from baseline in patients' best VA, considered the most relevant for clinical practice in the CS, compared patients' better seeing eye at baseline with the VA in patients' better seeing eye at week 24 even if the better-seeing eye at week 24 was not the same as the better-seeing eye at baseline. Please provide the number of participants in each group whose best seeing eye changed from one to the other between baseline and follow-up. Please provide this data for participants across studies (EAP, LEROS, CaRS I and II) if available.

A response to A22 will be shared on 12th December.

A23. In CaRS I, patients were eligible for the Natural History Outcomes Population if they had greater than or equal to three VA assessments available 24 months post progression. Please comment on the likelihood of this introducing a selection bias into the Natural History Outcomes Population, i.e., patients who have more visits have a worse trajectory than patients not attending.

We consider in all likelihood the opposite is the case. If a patient has stable vision loss and no option of treatment to alleviate this, they are less likely to return for ongoing assessment. LHON is characterised by a **painless, fast progressing and severe,** loss of visual function. The majority of LHON patients don't present any other symptomatology than ocular. Before the availability of specific therapy (idebenone) or clinical trials (specially gene therapy) patients were told about the poor prognosis and the rarity of spontaneous recovery. Thus, in the absence of extraocular features and/or pain, and with such a bad prognosis plus lack of treatment, patients would not have any reason to return to regular visits to the neuro-ophthalmologist. In fact, it would be those that show some degree of spontaneous recovery the ones returning to the ophthalmology clinic, so the specialist can confirm the improvement and maybe improve the prognosis.

Another factor to consider is the belief (until the availability of idebenone) that affected retinal ganglion cells were in their majority apoptotic after already 12 months since symptom onset, so that once reached this stage (canonically considered as "chronic") the chances of improvement were considered, if any, very low. Traditionally, 5 years

from symptom onset has been considered the limit after which all affected cells will have gone into apoptosis and the function irretrievably lost.

The above considerations explain why in the absence of any signs of improvement, affected patients would have no drive to return to regular visits, especially after 12 months since onset. In fact, the above explanations support that most probably, the bias would be in favour of spontaneous responders having more visits than non-responders.

HRQoL

A24. From RHODOS, please provide a scatterplot of patients' VF-14 against the best VA at each time point.

A response to A24 will be shared on 12th December.

A25. From RHODOS, please provide the results of a mixed-effects model predicting VF-14 with the best VA (fixed effect), treatment (fixed effect) and patient ID (random effect). If deemed appropriate, please also include the visit and the interaction of treatment by visit in the model.

A response to A25 will be shared on 12th December.

Safety

A26. Please provide a summary of the safety data from the post-authorisation observational study PAROS trial

The safety evidence from the PAROS trial demonstrates that the long-term administration of idebenone for the treatment of LHON was well-tolerated and no new safety concerns were observed. Overall the incidence of adverse events of special interest (AESIs) and adverse events (AEs) was low.(50)

A summary of the safety data from PAROS is captured below. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The AEs were tabulated by Preferred Term (PT) and by System Organ Class (SOC).

Frequency of adverse events of special interest

The treatment emergent AESIs are summarised in Table 11.

Table 11. AESIs by SOC and PT (safety population)

System organ class Preferred term	Events	Patients	Days in treatment*	
			Mean (SD)	Min - max
Total AESIs and patients with AESIs	58 (100.0%)	25 (11.2%)	413.8 (271.4)	0 - 1084
Blood and lymphatic system disorders	9 (15.5%)	8 (3.6%)	410.8 (268.4)	13 - 978
Anemia macrocytic	2 (3.4%)	2 (0.9%)	258.0 (69.3)	209 - 307
Macrocytosis	2 (3.4%)	2 (0.9%)	191.5 (252.4)	13 - 370
Anemia	1 (1.7%)	1 (0.4%)	555.0 (NA)	555 - 555
Leukopenia	1 (1.7%)	1 (0.4%)	361.0 (NA)	361 - 361
Neutropenia	1 (1.7%)	1 (0.4%)	361.0 (NA)	361 - 361
Neutrophilia	1 (1.7%)	1 (0.4%)	978.0 (NA)	978 - 978
Thrombocytopenia	1 (1.7%)	1 (0.4%)	543.0 (NA)	543 - 543
SOC Investigations	48 (82.8%)	21 (9.4%)	411.6 (276.9)	0 - 1084
Alanine aminotransferase (ALT) increased	18 (31.0%)	15 (6.7%)	350.9 (289.7)	0 - 1084
Gamma-glutamyl transferase (GGT) increased	18 (31.0%)	15 (6.7%)	439.6 (250.1)	1 - 811
Aspartate aminotransferase (AST) increased	11 (19.0%)	9 (4.0%)	452.3 (315.2)	1 - 1084
Liver function test abnormal	1 (1.7%)	1 (0.4%)	555.0 (NA)	555 - 555
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (1.7%)	1 (0.4%)	543.0 (NA)	543 - 543
Chronic myeloid leukemia	1 (1.7%)	1 (0.4%)	543.0 (NA)	543 - 543

*Days since start of treatment (date of first dose of idebenone) at time of event.
Abbreviations: AE – Adverse event; ALT – Alanine aminotransferase; AST – Aspartate aminotransferase; GGT – Gamma-glutamyl transferase; NA – Not applicable; PT – Preferred term; SD – Standard deviation; SOC – System organ class.

Frequency and nature of adverse events

A total of 382 AEs was reported by 130 patients in the safety population during the study. Table 12 summarises the AEs by SOC and PT reported by >5% of patients in the safety population.

Table 12. Adverse events reported by >5% patients (safety population)

System organ class Preferred term	Events	Patients	Days in treatment*	
			Mean (SD)	Min - max
Total AEs and patients with AEs	382 (100.0%)	130 (58.0%)	388.7 (323.8)	0 - 1450
Gastrointestinal disorders	41 (10.7%)	24 (10.7%)	216.0 (229.0)	0 - 833
Diarrhea	17 (4.5%)	15 (6.7%)	163.9 (211.9)	0 - 827
General disorders and administration site conditions	37 (9.7%)	34 (15.2%)	384.5 (299.6)	0 - 1161
Drug ineffective	27 (7.1%)	27 (12.1%)	433.4 (267.9)	0 - 1111
Investigations	58 (15.2%)	29 (12.9%)	390.6 (270.7)	0 - 1084
Alanine aminotransferase (ALT) increased	18 (4.7%)	15 (6.7%)	350.9 (289.7)	0 - 1084
Gamma-glutamyl transferase (GGT) increased	18 (4.7%)	15 (6.7%)	439.6 (250.1)	1 - 811
Metabolism and nutrition disorders	46 (12.1%)	36 (16.1%)	512.9 (352.7)	3 - 1441
Vitamin D deficiency	18 (4.7%)	17 (7.6%)	489.5 (370.3)	3 - 1441
Folate deficiency	13 (3.4%)	13 (5.8%)	591.1 (389.6)	167 - 1317
Other AEs				
Eye disorders	30 (7.9%)	22 (9.8%)	346.0 (260.0)	5 - 911
Infections and infestations	29 (7.6%)	18 (8.0%)	375.8 (333.4)	0 - 1359
Injury, poisoning and procedural complications	19 (5.0%)	17 (7.6%)	559.9 (434.6)	30 - 1420

*Days since start of treatment at time of event.
Abbreviations: AE – Adverse event; ALT – Alanine aminotransferase; AST – Aspartate aminotransferase; GGT – Gamma glutamyl transferase; SD – Standard deviation.

Adverse events leading to discontinuation of idebenone

A summary of the AEs leading to discontinuation of idebenone treatment are shown in Table 13. A total of 34 (15.2%) patients reported 38 AEs that led to discontinuation of idebenone treatment. These occurred at a mean of 350.9 days in treatment. The majority of patients (29 [12.9%]) reported mild AEs; moderate or severe AEs were reported by 4 (1.8%) patients each. Thirty-two SAEs and 58 AESIs were reported by 26 (11.6%) and 25 (11.2%) patients, respectively.

Table 13. AEs leading to treatment discontinuation, SAEs and AESIs (safety population)

Category	Events	Patients	Days in treatment*	
			Mean (SD)	Min, max
AEs leading to permanent discontinuation of idebenone	38 (100.0%)	34 (15.2%)	350.9 (272.2)	0 - 1111
Mild	31 (79.5%)	29 (12.9%)	371.4 (277.9)	0 - 1111
Moderate	4 (10.3%)	4 (1.8%)	295.3 (300.6)	118 - 743
Severe	4 (10.3%)	4 (1.8%)	252.8 (236.4)	0 - 543
SAE	32	26 (11.6%)	461.8 (407.7)	0 - 1399
AESI	58	25 (11.2%)	413.8 (271.4)	0 - 1084

*Days since start of treatment at time of event.
Abbreviations: AE – Adverse event; AESI – Adverse event of special interest; SAE – Serious adverse event; SD – Standard deviation.

Subgroup Data

A27. Priority. The EAG's clinical experts noted it is plausible that the benefit a patient may receive from idebenone treatment may be largest if they are treated prior to nadir, but noted the lack of available data to support this. The EAG notes that the company subgroup analyses of patients <1 year since symptom onset vs >1 year since symptom onset do not suggest an interaction between treatment and time since symptom onset, but the EAG notes that:

a) **The clinical trials were not powered to detect subgroup effects, and;**

b) **Dichotomising patients around 1 year since symptom onset is unlikely to be a powerful test of the interaction between time since onset and treatment effect, as time since onset is a continuous predictor that may have a non-linear relationship with treatment effect.**

Please:

c) **Comment on whether the Company believes the clinical and cost-effectiveness of idebenone may be larger in a subgroup of patients**

treated either early on in the disease course, or with a baseline logMAR < 1.

d) **Provide the following scatterplots for RHODOS, LEROS and the EAP patients:**

- **Baseline best logMAR vs Last visit best logMAR;**
- **Time since symptom onset vs Last visit best logMAR.**

Please include separate graphs for idebenone treated patients (RHODOS, LEROS and EAP), placebo treated patients (RHODOS) and propensity score matched/weighted controls (LEROS).

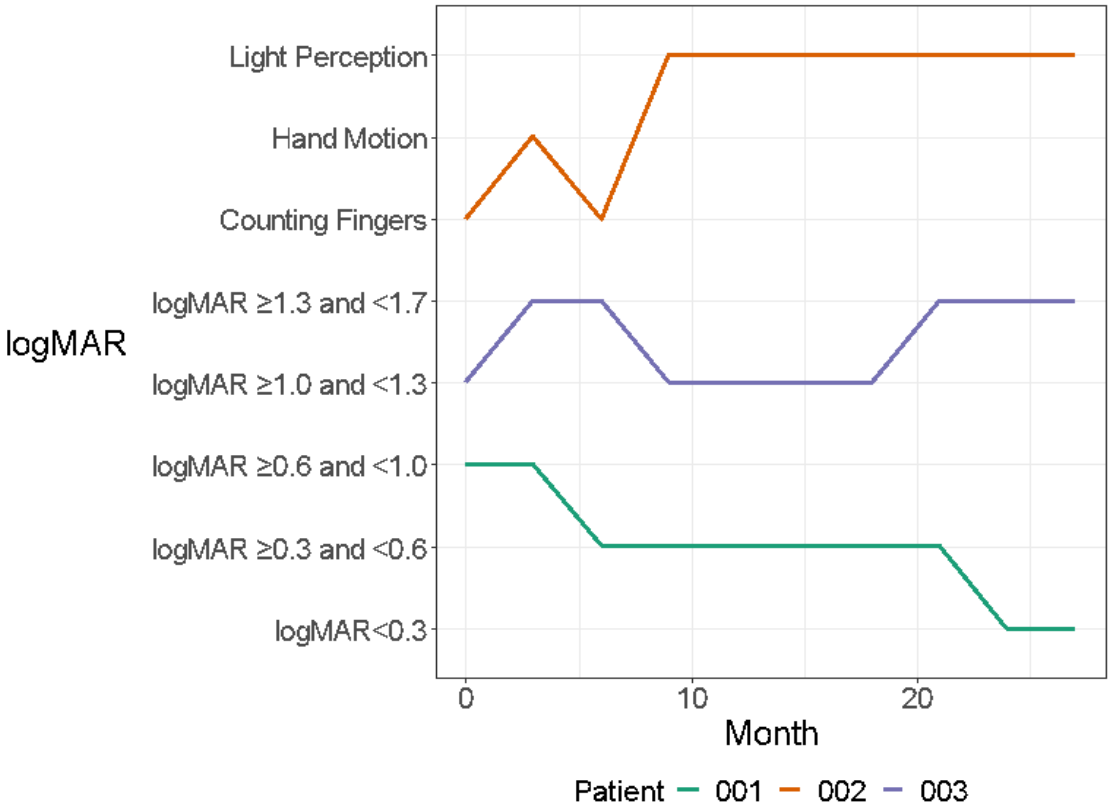
e) **Please provide appropriate regression analyses between: i) baseline logMAR and last visit best logMAR, and ii) time since symptom onset and last visit best logMAR for RHODOS and LEROS (propensity score matched analyses). For the time since symptom onset analysis, please consider using a non-linear model structure.**

A response to A27 will be shared on 12th December.

Individual Participant Trajectories

A28. Priority question. The EAG is concerned that the individual patient trajectories implied by using a Markov model might not reflect the individual patient trajectories observed in clinical trials, but notes these data have not been provided. Please provide the following graph by visit for patients in RHODOS idebenone and placebo patients (including OFU visit), EAP

idebenone patients and LEROS idebenone and matched-control patients. Please use a transparency value for the individual lines that overlap.



A response to A28 will be shared on 12th December.

A29. Priority question. Please complete the following tables for: i) RHODOS idebenone patients (including OFU visit); ii) RHODOS placebo patients (excluding OFU visit); iii) RHODOS idebenone patients (including OFU visit); v) EAP idebenone patients; vi) LEROS idebenone patients; vii) LEROS matched-control patients and vii) CaRS patients.

a) Change in logMAR from baseline

	LogMAR at final visit							
	<0.3	≥0.3 and < 0.6	≥0.6 and < 1.0	≥1.0 and < 1.3	≥1.3 and < 1.7	Hand Motion	Counting Fingers	Light Perception

LogMAR at baseline	<0.3								
	≥0.3 and < 0.6								
	≥0.6 and < 1.0								
	≥1.0 and < 1.3								
	≥1.3 and < 1.7								
	Hand Motion								
	Counting Fingers								
	Light Perception								

b) Change in logMAR from nadir

		LogMAR at final visit							
		<0.3	≥0.3 and < 0.6	≥0.6 and < 1.0	≥1.0 and < 1.3	≥1.3 and < 1.7	Hand Motion	Counting Fingers	Light Perception
	<0.3								
	≥0.3 and < 0.6								
	≥0.6 and < 1.0								
	≥1.0 and < 1.3								
	≥1.3 and < 1.7								

LogMAR at nadir	Hand Motion								
	Counting Fingers								
	Light Perception								

A response to A29 will be shared on 12th December.

Section B: Clarification on cost-effectiveness data

New company base case

Questions B6, B9, B11, B17, B18 and B19 resulted in updates being made to the cost-effectiveness model. The ICER and associated change from the CS ICER for each update are presented in Table 14. The updates result in a new base case ICER of £18,758.

The company would like to highlight that the company have also corrected the PSA error that the EAG kindly shared via email prior to receiving the clarification questions.

Table 14: A summary of the corrections and updates made to the base case CEA*

Question that the change relates to	Change	ICER*	Change from company submission base case ICER*
CS base case at submission		[redacted]	–
B6	The EAG's preferred half-cycle correction applied.	[redacted]	[redacted]
B9	Age-adjusted utilities applied to QALY calculations.	[redacted]	[redacted]
B11	Removed caregiver disutilities applied to the proportion of patients who received residential care	[redacted]	[redacted]
B17	Updated the cost of residential care to £1442 per week as sourced from PSSRU (2002)	[redacted]	[redacted]

B18	Applied a 'first visit' cost to the first ophthalmology visit per patient	[redacted]	[redacted]
B19	Apply the cost of OCT for each ophthalmology visit	[redacted]	[redacted]
New company base case		[redacted]	[redacted]

*Changes have compounding effect on the ICER and therefore values do not add to the total.
Abbreviations: EAG – Evidence review group; OCT – Optical coherence tomography; QALY – Quality-adjusted life year

The new company deterministic base case results (Patient Access Scheme [PAS] price) are presented in Table 15. For reference, the CS deterministic base case results (PAS) are presented in Table 16.

Table 15. New base case deterministic results (PAS price)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,758

Abbreviations ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; PAS – Patient access scheme; QALYs – Quality-adjusted life years; SoC – Standard of care

Table 16. CS base case deterministic results (PAS price)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,307

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; PAS – Patient access scheme; QALYs – Quality-adjusted life years; SoC – Standard of care

Model structure

B1. Priority question. The EAG considers that the current model is fundamentally flawed and inappropriate for decision making as there is insufficient evidence to support the high number of health states in the economic model given the modest differences in health-related quality of life and functional capabilities between some of the health states according to the EAG's clinical experts. The large number of health states in the economic model also significantly limits the available patient data used to inform the

transition probabilities, leading to some transitions being impossible and data imputation being required. For example, under both probabilistic and deterministic conditions it is impossible for idebenone treated patients to remain in the Hand Movement health state past cycle 10.

The EAG considers that these issues could be resolved by updating the model structure by grouping the health states as indicated in the table below, which outlines a similar model structure to that used in HST11. Please note that simplifying the model structure as suggested makes the best use of the available data and will impact the estimation of health state utility and health state resource use values. If the company agrees to the proposed updated model, the results calculated using the model with the company preferred assumptions would then represent the company's new base case and the EAG scenario requests outlined in section B would need to be conducted using the new model.

In the unlikely event that the company considers the current model "robust", the EAG requests that they provide the recommended new model as a scenario to assess the structural uncertainty identified by the EAG in the current model.

Company health states	EAG preferred health states
LogMAR <0.3	Limited visual acuities
LogMAR 0.3-0.6	Moderate visual acuities
LogMAR 0.6-1.0	
LogMAR 1.0-1.3	On chart visual acuities
LogMAR 1.3-1.7	

CF	Off chart visual acuities
HM	
LP	

The company strongly considers the base case model to be adequately robust and clinically and economically plausible for decision making in patients with LHON. This model has undergone extensive validation by clinical experts in LHON and numerous other HTA bodies globally, captures the natural progression of LHON, and aligns with models structures similar to those seen in previous NICE technology appraisal (TAs) (TA274, TA283, TA298).(51–53) Furthermore, the CEA is limited by the ultra-rarity of LHON and subsequently low patient numbers. Therefore, the company consider that the most robust approach for this CEA has been taken.

The current model structure robustly captures the natural progression of LHON over time

Eight distinct health states based on VA were selected to form this model structure in order to capture the true clinical and economic burden of LHON. The impact of the small changes in LogMAR ranges for each health state has a substantial difference on the daily functioning of patients with LHON which translates into QoL benefits and cost savings. Combining these distinct LogMAR ranges together into single health states will not accurately capture the costs and effects modelled for patients with LHON and therefore fail to robustly evaluate the cost-effectiveness of idebenone.

In Brown et al. (1999), utility values were derived based on VA levels with 0.1-0.2 LogMAR differences.(54) The study administered a visual function test consisting of 22 questions on basic activities for functioning in life, social issues, emotional or psychological issues, and activities of employment. Brown et al. reported that as each VA level decreased, the corresponding visual function test score also decreased across all levels. The greatest absolute decreases in total mean function test score occurred in between the VA levels corresponding to LogMAR 0.4 to LogMAR 0.6,

LogMAR 0.6 to LogMAR 0.8 and CF to HM/LP. Therefore, it would be clinically inappropriate to group these LogMAR ranges together into single health states as the differences in QoL between LogMAR VA will not be accurately captured in the CEA, creating highly uncertain cost-effectiveness results.

Significant differences were identified in the KOL survey in resource utilisation between small LogMAR changes. For example, clinicians estimated that 39% of patients in the LogMAR 0.3-0.6 health state would require outpatient care compared to 80% in the LogMAR 0.6-1.0 health state and that no patients would require supportive living care in the LogMAR 0.3-0.6 health state compared to 20% in the LogMAR 0.6-1.0 health state. Similarly, they estimated that 45% of patients in the CF health state would accrue costs due to depression compared to the 65% of patients in the HM health state. These varying levels of resource use uptake for each health state translates into wide-varying total costs. Therefore, grouping health states together would inaccurately capture the cost of LHON in patients across varying levels of VA and subsequently inaccurately capture the cost-savings introduced by idebenone.

The model has been extensively validated and uncertainty explored

Clinical experts in LHON agreed that the health states included in the company's model structure fully capture the clinical and economic burden of LHON (Appendix N of the CS). Furthermore, this model has undergone extensive validation, and was subsequently accepted, by numerous other HTA bodies, including SMC, AWMSG and NCPE. (11–13)

Resource use inputs for each health state in the CEA were informed by numerous KOLs who specialise in ophthalmology and were then later validated by UK clinical experts in LHON. Each input was informed using the company's original health states. For inputs where UK clinical experts have suggested small changes, scenario analyses have been conducted (see Section B.3.11.3 of the CS) which have a small impact on the ICER.

Health-related quality of life (HRQoL) values were informed using published literature and aligned with HRQoL used in numerous other previous NICE TA appraisals. Multiple published sources have been explored as scenarios which have a small

impact on the ICER. Base case HRQoL values were informed by Brown *et al.* (1999) which assessed the quality of life (QoL) associated with small variations in VA.

The company's model structure aligns with previous NICE TAs

Furthermore, the company's model structure aligns with the model structure demonstrated in TA274, TA283 and TA298 (51–53), where up to 9 health states were defined by the ETDRS letter scale (Section B.3.2.2.1). The economic analyses in these TAs were based on clinical data which consisted of a similar number of patients to this appraisal; TA298 and TA274 included only N=116 patients in the intervention arm.

Whilst HST 11 may include a reduced number of health states, as highlighted by the EAG, there are substantial differences in the modelled population and distribution of patients compared to the company submission.

HST 11 only models patients who are classified as blind (LogMAR > 1) and health states for patients with VA of LogMAR < 1 were not included. As a result of not modelling VA across such a large LogMAR range, the health states included in the economic analysis of HST 11 are still only defined by small LogMAR ranges. For example, in HST 11, 'HS2' is defined as 1.0 ≤ LogMAR < 1.4 and 'HS3 is defined as 1.4 ≤ LogMAR <1.8. However, in the EAG's proposed health states for this appraisal, patients would be grouped based on large varying LogMAR values ('Moderate visual activities' [MVA]: 0.3 ≤ LogMAR ≤ 1.0; 'On chart visual activities' (OnVA): 1.0 < LogMAR ≤ 1.7). Given the small patient numbers included in this CEA, these broadly defined health states may mean that there is high heterogeneity in outcomes observed for each health state which adds uncertainty to model estimates. Furthermore, as detailed above, differing QoL values and resource use are demonstrated within varying small LogMAR ranges which would not be accurately captured within the large LogMAR ranges proposed by the EAG.

Furthermore, HST 11 states that due to few recorded observations in the natural history data that was used, the HM, LP and NLP (no light perception) states were grouped together into one health state, 'HS5'. In HST 11, only 3% of patients were in this grouped health state at baseline. In comparison, in the company model, an

average of [redacted]% of patients (n=[redacted]) across the RHODOS, EAP and CaRS studies make up the EAG's proposed combined health state of 'Off chart visual acuities' (OffVA), consisting of CF, HM and LP, which is a substantial proportion of the model population with varying levels of VA.

Limitations of rare diseases

Given the ultra-rarity of LHON (55), data are limited and the number of patients partaking in clinical trials remains low; 85 patients across idebenone and placebo treatment arms in RHODOS, 87 patients in the idebenone arm in the EAP study and 74 patients in the CaRS were included in the CEA. Whilst this may still present a large percentage of patients with LHON, it is a low sample size for the CEA and explains the limitations in data for informing some health states at certain time points. This is a common occurrence when modelling rare diseases and the company have ensured that the most appropriate clinical data has been utilised and explored the uncertainty through deterministic and probabilistic sensitivity analyses and scenario analyses.

Whilst the EAG highlight that the company's health states require data imputation to inform selected transition probabilities, this still occurs when using the EAG's proposed health states. For example, data imputation is still required for LogMAR <0.3 in the idebenone arm for 18 months – 24 months and again at 27 months to 33 months. Therefore, low patient numbers due to the rarity of the disease will continue to be a limitation.

The company therefore believe that the current model structure is the most robust and appropriate for decision making and maintain this approach in the base case economic analysis.

Scenario using the EAG's proposed health states

However, in order to facilitate the EAG in their assessment, the company have explored a scenario adopting the EAG's proposed health states.

The company carried out a naïve scenario in which clinical data, HRQoL and resource use inputs were grouped to align with the proposed health states but applied to only

one health state per group in the model (no structural changes were carried out). The approach was carried out using the company's base-case assumptions.

Clinical data

Patient counts were summed together for each proposed health state for each cycle in each treatment arm. Table 17 demonstrates the calculations conducted to obtain patient counts for the aggregated health states: patient counts in each yellow rectangle that were summed together and then assigned to aggregated health states in the company's model, using the patients counts from baseline to month 3 in the idebenone arm as an example. Patient counts for the idebenone arm were informed using RHODOS from baseline to month 3 and EAP from month 6 to month 36 and patient counts for the SoC arm were informed using RHODOS from baseline to month 3 and CaRS from month 6 to month 36.

Table 17. An example of the changes made to the patient counts to align with the EAG's proposed health states (baseline – month 3 in the idebenone arm)

Patient counts in the company's current model structure

	LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6-1.0	LogMAR 1.0-1.3	LogMAR 1.3-1.7	CF	HM	LP	Total
LogMAR <0.3	[redacted]								
LogMAR 0.3-0.6	[redacted]								
LogMAR 0.6-1.0	[redacted]								
LogMAR 1.0-1.3	[redacted]								
LogMAR 1.3-1.7	[redacted]								
CF	[redacted]								
HM	[redacted]								
LP	[redacted]								

Patient counts in the scenario exploring the EAG's proposed health states

	LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6-1.0	LogMAR 1.0-1.3	LogMAR 1.3-1.7	CF	HM	LP	Total
LogMAR <0.3	[redacted]								
LogMAR 0.3-0.6	[redacted]								
LogMAR 0.6-1.0	[redacted]								
LogMAR 1.0-1.3	[redacted]								
LogMAR 1.3-1.7	[redacted]								
CF	[redacted]								
HM	[redacted]								
LP	[redacted]								

Abbreviations: CF – Counting fingers; HM – Hand motion; LP – Light perception

HRQoL

The same HRQoL values were applied to each of the health states which were grouped into one of the EAG's proposed health states. HRQoL values were calculated based on an average of the combined health states. Table 18 demonstrates the HRQoL values derived from Brown *et al.* used in the company's scenario. For further scenarios of the EAG's proposed health states using the alternative HRQoL sources, see the company's response to Question B10.

Caregiver disutilities were already aligned with the EAG's proposed health states and therefore were not updated.

Table 18. HRQoL values calculated based on the EAG's proposed health states

Health state	Utility values
LogMAR <0.3	0.840
LogMAR 0.3-0.6	0.720
LogMAR 0.6-1.0	0.720
LogMAR 1.0-1.3	0.585
LogMAR 1.3-1.7	0.585
CF	0.407
HM	0.407
LP	0.407

Abbreviations: CF – Counting fingers; HM – Hand motion; LP – Light perception

Resource use

Similar to the approach with HRQoL values, the same resource use inputs were applied to each of the health states which were grouped into one of the EAG's proposed health states. The proportions of patients for each of the proposed health states were calculated based on an average of the combined health states and informed using the KOL survey.(Table 19)

Table 19. Resource use calculated based on the EAG's proposed health states

Resource	LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6-1.0	LogMAR 1.0-1.3	LogMAR 1.3-1.7	CF	HM	LP
Hospitalisation	2%	7%	7%	19%	19%	26%	26%	26%
Outpatient care	13%	59%	59%	83%	83%	83%	83%	83%
Community care - Blind registration	0%	52%	52%	100%	100%	100%	100%	100%
Community care - supportive living	0%	10%	10%	44%	44%	63%	63%	63%
Residential care	0%	4%	4%	8%	8%	26%	26%	26%
Depression resulting from LHON	7%	25%	25%	38%	38%	56%	56%	56%

Abbreviations: CF – Counting fingers; HM – Hand motion; LHON – Leber's hereditary optic neuropathy; LP – Light perception

Results

The deterministic scenario results using the EAG's proposed health states for idebenone vs SoC are presented in Table 20. The scenario is applied to the new company base case detailed in Table 15. This has led to a minimal increase in the ICER of £8,296, from £18,758 to £27,053. This increase in the ICER suggests it still falls below the cost-effectiveness threshold of £30,000. However, due to the clinically implausible grouping of health states, this ICER is not a true representation of the cost-effectiveness of idebenone.

Table 20: Deterministic scenario results using the EAG's proposed health states (PAS price)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
SoC	[redacted]	[redacted]	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	27,053

Abbreviations: ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life-years; SoC – Standard of care

B2. Priority question. In Section B.2.2, the Company states that results from LEROS, "have not been included in the economic model due to heterogeneity between the patient populations" and, in Section B.3.3.2 that there were concerns about, "generalisability to patients in UK clinical practice". Please describe:

a) **In detail, the heterogeneity between LEROS and other included studies, and why LEROS itself is considered an outlier when many of its key baseline characteristics (baseline logMAR, time since onset of symptoms) are more closely aligned to the primary RCT than the other studies?**

b) **Outline which specific characteristics in LEROS the Company considers are not generalisable to UK clinical practice. Please include evidence that these characteristics in LEROS are meaningfully different from UK clinical practice and provide evidence that these characteristics are either important prognostic factors or treatment effect modifiers.**

In the CS model, the RHODOS trial was used to model the efficacy of idebenone in the first six months. The trial was chosen because it was the only randomised, double-blind, placebo-controlled, multicentre study to evaluate the clinical effectiveness of idebenone for treating LHON. However, the 24-week duration of the RHODOS trial was insufficient to fully demonstrate the benefits of idebenone on patients with LHON. Therefore, the EAP data was selected to model the long-term extrapolation of idebenone efficacy beyond the initial six months. The reasons for selecting the EAP study instead of the LEROS trial are described below.

The company considers it appropriate to exclude the LEROS data from the economic model due to the lack of similarities with the RHODOS trial population. The RHODOS trial consisted of idebenone-treated patients who carried the three mutations of LHON (G11778A [67.1%], T14484C [20%], G3460A [12.9%]), whilst the ITT population within LEROS consisted of patients from a wider range of LHON mutations (G11778A [57.1%], T14484C [17.3%], G3460A [17.9%], Negative [5.1%], Other [2.6%]). UK clinicians noted that the G11778A mutation may be under-represented in the LEROS trial population.(56) Whereas the EAP study, has a much more similar mutation distribution to RHODOS compared to LEROS; (G11778A [62.1%], T14484C [18.4%], G3460A [19.5%]).

Furthermore, input from clinical experts suggests that different mutations may have a different impact on outcomes stating that patients with the T14484C mutation show a higher rate of spontaneous recovery.(56) One of the clinical experts also noted that the G11778A mutation is more common in the RHODOS trial population (approximately 67% of patients) than in the LEROS trial population (approximately 55% of patients) and he believed that the G11778A mutation was slightly under-represented in the LEROS trial population.(56) The imbalances in mutation type between RHODOs AND LEROS may lead to a bias in efficacy results. Additionally, the LEROS trial had a smaller proportion of male patients within the ITT population (73.5%) compared to RHODOS (85.9%) and given that ~80-90% of LHON cases typically occurs in males, this may be an under-representation of the patient population seen in clinical practice. (6) However, the EAP study demonstrates a proportion of males included in the study closer to the proportion seen in the RHODOS study and clinical practice; 82%.

The Company considers the EAP to be the best source of long-term effectiveness for the economic model. This is due to the longer trial duration, spanning 36-months, compared to the LEROS trial, which was 24-months. Given that LHON is a rare disease, where data availability is already limited, the Company considers this longer follow up period essential in reducing any uncertainty in the economic modelling. This three-year follow up period aligns with the treatment duration expected by UK clinicians. Based on expert opinion, patients will be treated for one year before assessing a response, and then a further two years until VA stabilised, summing to a total of three years.(56)

In the recently published NICE RWE framework, it is stated that the RWE could be used more routinely to fill evidence gaps and speed up access for patients where RCTs and non-randomised studies cannot, further supporting the use of the EAP. The updated NICE strategy 2021 to 2026 also aims to use real-world data to resolve gaps in knowledge and drive forward innovation.(57) Furthermore, data from EAP has been used to support the long-term economic modelling of idebenone in other UK HTA submissions including SMC, AWMSG and NCPE.(11–13)

c) **Conduct a scenario using the LEROS patient data to inform the idebenone treatment patient transition probabilities after 6 months. Please use the LEROS ITT population in addition to any sub populations the company prefers.**

To support the EAG in their assessment of this appraisal, the company have provided a scenario using the LEROS data.

Treatment effectiveness sources

The following data sources were evaluated to inform the transitions between the logMAR health states:

- First 6 months, idebenone and SoC (no changes compared to the original CS): The RHODOS study [N=85 safety population; N=82 efficacy population]: enrolled patients that had experienced vision loss due to LHON within 5 years

(mean time since onset of symptoms was 22.8-months). LogMAR was collected for idebenone and placebo patients at baseline, 3-months and 6-months. (10)

- Extrapolation after 6 months, idebenone: The LEROS study [N=87 ITT population]: see below for description of data collection. Standardised follow-up is available for up to two years.(58)

- Extrapolation after 6 months, SoC (no changes compared to the original CS): The CaRS studies [N=74 Natural history outcomes population not treated with idebenone (which forms the efficacy population of this analyses) and N=188 with previous idebenone use]: collected historically documented VA data from existing medical records in 11 participating clinical centres (10 Europe, 1 US). No inclusion criteria were specified, and data were collected non-systematically, without pre-selection, based on participating clinical centres record-keeping practices. (48) Despite not being identified in the SLR, the results of the CaRS study are included in the economic modelling in the SoC arm as they demonstrate the disease course of LHON in patients who only received SoC.

In the LEROS trial, patients level data were collected at months 6, 9, 12, 18 and 24, hence missing month 15 and 21 used in the model. Patient counts from month 12 were assumed for month 12-15 and 15-18 in the model, similarly the patient counts from month 18 were used for month 18-21 and 21-24. Patients are assumed to remain in the same health state from month 24 onwards. In the Company base case where EAP is used, this assumption was implemented from month 36, due to longer trial duration. Where data does not exist for the transition of patients in a certain health state at a certain time point, patients are assumed to remain in the same health state.

The Natural History matched controlled comparator could not be used to inform transition probabilities for SoC in the economic model. This is due to the matching algorithm being performed de novo at each time point. This implies that the same patient is not necessarily followed over the trial duration as the matching was performed on eyes (not patients), and therefore, their movement across health states

cannot be accurately captured. Given this, the CaRS study has been utilised to inform the SoC arm of the model beyond six months.

This means that we do not necessarily follow the same patient over the trial duration, especially as the matching was performed on eyes (not patients), and therefore cannot accurately capture their movements across health states. Given this, we have used the CaRS study to inform the SoC arm of the model beyond six months.

Intervention and comparator's cost and resource use

Treatment costs for idebenone are calculated based on the three-monthly acquisition cost of treatment, multiplied by the compliance and persistence of idebenone. No administration costs are considered since idebenone is an oral treatment.

A compliance rate of 96% has been used, as per the RHODOS study. Persistence data that were available for idebenone from the LEROS study were considered to inform the duration of treatment with idebenone.

Figure 2. LEROS ITT persistence KM

For each cycle, the three-monthly cost of treatment (£[redacted] – PAS price) is multiplied by the compliance rate (96%) and cycle-specific persistence rate using the Kaplan Meier estimator to generate the treatment costs per cycle.

Comparator (SoC) and resource use costs remain aligned with the CS, see Section B.3.5 for more details.

Results

The deterministic scenario results when applying LEROS data from month 6 to month 24 in the idebenone arm are presented in Table 21. The scenario is applied to the new company base case detailed in Table 15. This has led to an increase in the ICER of £2,551, from £18,578 to £21,129.

Table 21: Deterministic scenario results using RHODOS and LEROS data in the idebenone arm (PAS price)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
SoC	[redacted]	[redacted]	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	21,129

Abbreviations: ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life-years; SoC – Standard

B3. Priority question. The CS states that a last observation carried forward (LOCF) approach was applied to the CaRS dataset, used to inform the transition probabilities of the SoC arm. Please can the company;

a) explain why LOCF was not similarly applied to the EAP dataset, used to inform the idebenone patients;

The company used the LOCF in the CaRS data set due to the low patient numbers in the later follow-up time points. LHON is of a progressive nature and the lack of treatment able to tackle the underlying genetic condition, prevent VF loss or aid recovery, means SoC patients are not expected to improve in VA. Given this, it was considered a conservative assumption to carry forward observations in the CaRS data. If LOCF was not applied, patients likely would transition to more severe health states due to progressive nature of disease. Without the LOCF approach, the patient

numbers in the SoC arm would remain small across the 36 months of transition probabilities and resulted in considerably uncertainty, impacting the ICER.

The company do not consider the LOCF approach to be an accurate approach in modelling clinical effectiveness in patients treated with idebenone. The LOCF is overly conservative and biased against idebenone as it unrealistically assumes that patients cannot improve their VA beyond the point of their last follow-up, which may not be clinically accurate. This assumption is supported by the RHODOS-OFU study, where best VA continued to improve even after treatment with idebenone had ended. (1,59) Inclusion of LOCF in the idebenone arm would be especially biased against patients with shorter follow-up (e.g < 6 months) as it does not account for the likely future gains in VA that would happen if the patients were tracked over a longer timeframe after treatment with idebenone. Therefore, the company did not consider it clinically appropriate to apply the LOCF to the EAP patient counts in the idebenone arm and instead only apply it to the CaRS data to supplement the low patient numbers.

b) state how many of the observations used to calculate the transition probabilities were generated using LOCF;

Table 22 details the number of patients where follow-up was not available at each timepoint for the CaRS data. Please note that the proportion of patients missing observations at one timepoint may not be the same patients who are missing an observation at another timepoint. Patients need consecutive observations at each timepoint in order to be included in patient counts per cycle.

Table 22. Number of patients whose observations were LOCF at each timepoint in the CaRS data

Timepoint	Number of patients whose observations were LOCF at each timepoint (%)
Baseline	0 (0%)
Month 3	21 (28.4%)
Month 6	35 (47.3%)
Month 9	48 (64.9%)
Month 12	59 (79.1%)
Month 15	61 (82.4%)
Month 18	63 (85.1%)
Month 21	66 (89.2%)
Month 24	69 (93.2%)

Month 27	71 (95.9%)
Month 30	70 (94.6%)
Month 33	71 (95.9%)
Month 36	71 (95.9%)

Abbreviations: CaRS – Case Record Survey; LOCF – Last observation carried forward

c) conduct a scenario assuming data missing at random instead of LOCF

The company have explored a scenario where no LOCF is assumed in the CaRS data in the SoC arm. The deterministic scenario results when removing the LOCF assumption from the CaRS data for idebenone vs SoC are presented in Table 23. The scenario is applied to the new company base case detailed in Table 15. This has led to a substantial decrease in the ICER of £16,795, from £18,758 to £1,963.

Table 23: Deterministic scenario results removing the LOCF assumption from the CaRS data (PAS price)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
SoC	[redacted]	[redacted]	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	1,963

Abbreviations: ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life-years; SoC – Standard of care

B4 Priority question. Please can the company justify why SoC transition probabilities were not made probabilistic when conducting probabilistic sensitivity analyses? Please update the model so that SoC transition probabilities can be made probabilistic.

The company would like to thank the EAG for highlighting this in the model. Due to the ultra-rarity of LHON and the resulting low patient numbers, including the transition probabilities in the probabilistic sensitivity analyses creates substantial uncertainty in the probabilistic results of the CEA. Therefore, the transition probabilities for the idebenone and the SoC arm are not included in the probability sensitivity analyses.

The company would like to highlight that in order to explore the uncertainty in patient numbers in the CEA, the baseline distribution of patients are included in the deterministic and probabilistic sensitivity analyses as well as explored in the scenario analyses.

B5. As highlighted in clarification question A17 can the company explain the contrasting available patient data reported in Figure 1 in the EAP CSR and Figure 17 in the CS and the patient data used to calculated transition probabilities. For example, for the idebenone treated group, when calculating the transition probabilities from month 21 to month 24, data from 13 patients are used to inform the calculations while in Figure 17 in the CS data from 19 patients should be available and according to the Figure 1 in the EAP CSR data from 42 patients should be available.

Figure 17 of the CS details the proportion of patients at each time point that have a CRR, not the proportion who have recorded observations or the proportion who remain on treatment (as presented in Figure 1 of the EAP CSR).

The EAP study was a retrospective, non-controlled and open-label study. As the treatment duration was not predetermined but left at the treating physician's discretion, follow-up is very variable. Therefore, all patients who are still on treatment (as presented in Figure 1 of the EAP CSR) do not always have an observation recorded every three months.

Given the above, not every patient provides an observation at every timepoint of the EAP study. To derive a patient count, patients need to give observations at two consecutive timepoints (for example, an observation at month 21 and an observation at month 24) in order to track what state a patient has moved from and to. For example, 18 observations are provided at month 21 and 20 observations are provided at month 24 but only 13 of these observations at these two timepoints were from the same patient. Hence, the number of patients used to inform patients counts may not align with the number of patients still on treatment at that time point.

B6. The EAG notes that the half cycle correction has been incorrectly calculated as the average of the current and subsequent cycle, applied from the first model cycle (cycle 0), as opposed to the current and previous cycle, applied from cycle one onwards. Please could the company amend this in the economic model.

The company would like to note that the application of the half-cycle correction (HCC) in the economic model as part of the company submission, that is, calculating the average of the current and subsequent cycle, aligns with numerous other models

submitted as part of NICE technology appraisals (TAs), and therefore, do not consider it to be incorrect. However, for full alignment with the EAG, the company have updated the HCC calculation in the model to be calculated as the average of the current and previous model cycle applied from cycle 1 onwards.

This has led to a £241 minimal increase in the CS base case ICER from £20,307 to £20,548. The new company base case is detailed in Table 15.

Treatment effectiveness

B7. Priority question. As the long-term treatment effects of idebenone are uncertain and this uncertainty is not captured by the modelling assumption that VA if fixed till death after three years of treatment, please;

a) **conduct a scenario in which idebenone patient VA wanes to that of SoC patients at 5, 10, 20 and 30 years.**
b) **If the company considers that patients would be re-treated in clinical practice on VA decline, conduct an additional scenario exploring VA decline and retreatment for the idebenone treated patients.**

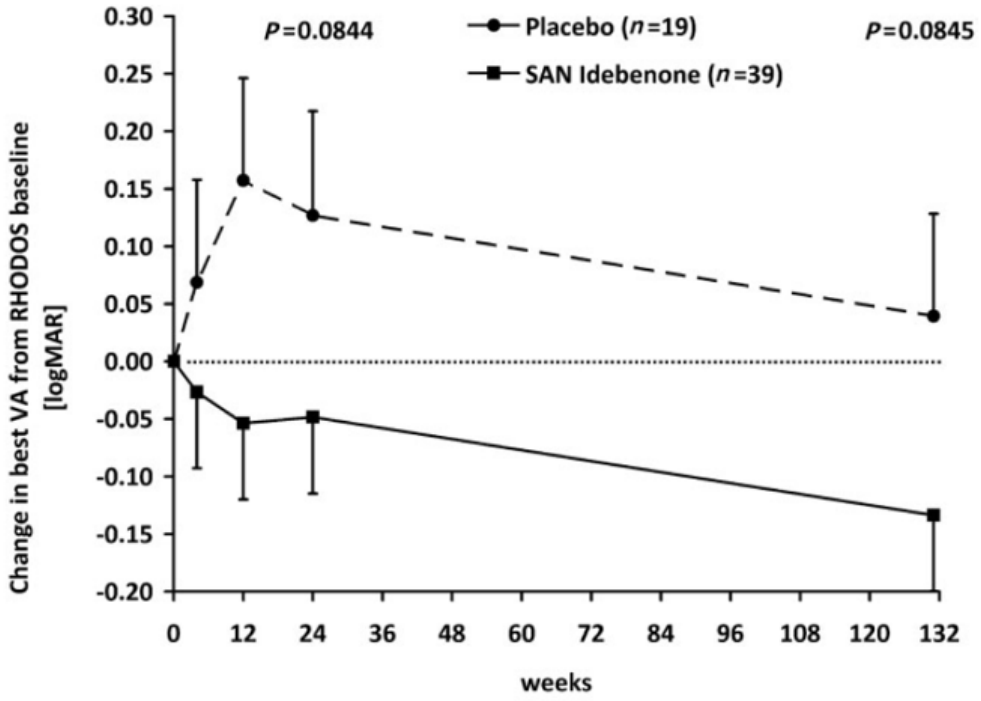
Based on evidence from the RHODOS-OFU trial and feedback from clinical experts, the company does not consider treatment waning or retreatment of idebenone clinically plausible scenarios given the lack of supportive evidence.

RHODOS-OFU was a single visit, observational follow up study to RHODOS, where patients were invited to attend a visit to ascertain their current status of visual acuity following the discontinuation of idebenone treatment at the end of RHODOS. During the RHODOS-OFU study period, patients were not treated with idebenone. The median time that had elapsed between Week 24 (end of idebenone treatment) of RHODOS and the RHODOS-OFU was 30 months (range: 20.9 to 42.5 months; 131 weeks).(1,60)

Best VA at the RHODOS-OFU visit improved in the idebenone group (mean change in logMAR -0.134, corresponding to an improvement of six letters).(1,59) The benefit of idebenone was maintained in this off-medication period (i.e. after Week 24 of the RHODOS trial) with a difference of logMAR −0.173 (8 letters); p=0.0845 between

treatment groups from baseline in RHODOS to RHODOS-OFU favouring idebenone (Figure 3).(60,61)

Figure 3. Change in visual acuity over time for the best visual acuity (logMAR)



Data are estimated means ± SEM from MMRM, based on the change from baseline (in weeks) and plotted for the two treatment groups as defined in the RHODOS study. No treatment was given between Week 24 and Week 131. Worsening/improvement of visual acuity is indicated as positive/negative values in change of logMAR. A difference of logMAR 0.1 corresponds to five letters or one line on the Early Treatment Diabetic Retinopathy Study chart. The P-values are given for the difference between treatment groups.
Source: Klopstock T et al, 2013 (60)
Abbreviations: logMAR – Logarithm of the minimum angle of resolution; MMRM – Mixed-model of repeated measures; SEM – Standard error of the mean; VA – Visual acuity

Data from RHODOS-OFU showed that the difference between treatment groups for the entire period from baseline of RHODOS to the RHODOS-OFU visit (logMAR −0.173), was comparable with the difference observed at Week 24 of RHODOS (logMAR −0.175). The benefit observed in the idebenone treatment arm remained after patients stopped the treatment, after 24 weeks, during the non-treatment observation period of 2.5 years (30 months). The difference between idebenone and placebo remained stable confirming the maintenance of treatment benefit of idebenone after 24 weeks of treatment beyond 2.5 years without therapy.

Clinical data shows that the treatment effect of idebenone was maintained long after the termination of therapy. Furthermore, idebenone recipients who were 'off-chart' at RHODOS baseline and achieved clinically relevant recovery (CRR) at Week 24 maintained their response at the RHODOS-OFU visit. UK clinical experts agreed that the results from RHODOS-OFU demonstrated a long-term clinically meaningful benefit of treatment with idebenone. Clinicians also agreed that visual acuity would remain stable following cessation of idebenone treatment after three years of treatment.(56) Based on the clinical data and experts' option, the company assumed that long term efficacy will be maintained after idebenone discontinuation. The company does not consider inclusion of waning effect clinically plausible, thus this scenario was not provided.

As no decline in VA is expected, retreatment is not considered. Therefore, additional scenarios exploring VA decline and retreatment for the idebenone treated patients have not been conducted.

B8. Priority question. The CSR states that of the 111 patients enrolled in the EAP study, 12 patients discontinued treatment due to lack of efficacy. However, the economic model does not account for any treatment discontinuation due to lack of efficacy and instead only reduces treatment costs as a result of persistence in which patients retain the full treatment efficacy of Idebenone but not the costs. As a scenario include idebenone patient discontinuation which mirrors treatment persistence. If the company instead is able to use the IPD data to identify specific discontinuation due to lack of efficacy this data can be used instead.

The EAP report v5.0, dated 11th October 2018, does state that 12 patients out of the 111 patients enrolled did discontinue due to a lack of efficacy. The final EAP report dated 28th August 2019, however states that cumulatively, nine out of 111 patients permanently discontinued idebenone treatment due to the lack of efficacy, or occurrence of AEs, or a fatal outcome. These nine discontinued patients are captured with the EAP safety population (N=111).

The efficacy population is defined as the sub-population of the safety population who carried one of the 3 major LHON-causative mtDNA mutations, who had time since

onset at Baseline of less than 12 months in the most recently affected eye and for whom post-Baseline VA efficacy data were available. Therefore, measurements for patients who discontinued would still be included in the model, permitting the patient had observations at two consecutive timepoints. Whilst the proportion of patients who discontinued due to lack of efficacy from the efficacy population is unknown, the model does include patients who are not necessarily deriving any clinically relevant benefit (CRB). For example, in the efficacy population, at final observation, 40.2% of patients derived a clinically relevant benefit, implying that 59.8% did not. Therefore, there are patients in the model who are still accruing costs for idebenone over the treatment duration (up to three years), and not achieving any QALY gains.

Given this, the model does conservatively include patients who would likely discontinue following clinician assessment of response after one year of idebenone treatment. The model is accruing these additional costs for patients who may not receive idebenone treatment in clinical practice, whilst also tracking their lack of benefit in the model and keeping this subset of patients in the higher logMAR health states.

Despite the above, the Company have provided a scenario where we have assumed that 4% of patients discontinue idebenone treatment after two years. The Company have applied a discontinuation rate 4%, based on 4 patients experiencing lack of drug effect (n=1), drug effect incomplete (n=1) and drug ineffective (n=2) as per Table 13.2.2 in the EAP CSR. It was assumed that the 4% discontinuation rate (due to lack of efficacy) will be in addition to the persistence data already included in the model. It was assumed that patients who discontinue idebenone treatment will accrue SoC costs and QALY gain. The total costs of idebenone in this scenario (with 4% discontinuation rate) were calculated as an average of idebenone costs (without discontinuation) and SoC costs weighted by a proportion of patients who discontinue idebenone (4%). The same method was applied to total QALYs calculations for idebenone.

The deterministic scenario results applying a 4% idebenone treatment discontinuation rate for idebenone vs SoC are presented in Table 24. The scenario is applied to the new company base case detailed in Table 15. The scenario presents an increase in the ICER of £951, from £18,758 to £19,709.

Table 24 . Deterministic scenario results applying 4% idebenone discontinuation (PAS price)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
SoC	[redacted]	[redacted]	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	19,709

Abbreviations: ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life-years; SoC – Standard of care

Health related quality of life

B9. Priority question: The EAG notes that no adjustment to utility values has been made to account for reductions in quality of life with age. The NICE methods guide recommends using the Health Survey for England (HSE) 2014 dataset, as recommended by the DSU (Hernández Alava *et al.* 2022). Please include the age adjustment of utility values in the model using the HSE 2014 dataset in a revised base case.

The company would like to thank the EAG for highlighting this. Age-adjusted utilities have been added to the company model as recommended by the DSU (Hernández Alava *et al.* 2022).(62)

This has led to a £1,800 increase in the CS base case ICER from £20,307 to £22,106. The new company base case is detailed in Table 15.

B10. Priority question: Given the request outlined in clarification question B1, please calculate the health state utility values for each of the health states using Brown *et al.*, Lawrence *et al.,* Czoski-Murray *et al.* and Rentz *et al*. and present the results of using the alternative sources as scenario analyses.

As detailed in the company response to Question B1, the company strongly consider the current model structure to be robust for decision making and do not think it is appropriate to group together the existing health states utility values due to significant differences in QoL between them as detailed by clinical experts and in literature.(54,63) However, the company conducted a scenario exploring the EAG's proposed health states applied to the company's base case assumptions.

Details of how the HRQoL values were calculated based on the EAG's proposed health states, along with the adjusted utility values for Brown *et al.*, are given in the response to Question B1. Adjusted utility values for Lawrence *et al.*, Czoski-Murray *et al.* and Rentz *et al.* are given in Table 25.

Table 25. Adjusted utility values based on the EAG's proposed health states for each source

Health state	Company submission – base case	EAGs requested health states – simplified model structure				
	Brown et al. (1999)	Brown et al. (1999)	Lawrence *et al.* (2023) - EQ-5D-5L	Lawrence *et al.* (2023) - HUI-3	Lawrence *et al.* (2023) - TTO	Czoski-Murray (2009)	Rentz *et al.* (2014) (UK only)
LogMAR <0.3	0.840	0.840	0.786	0.838	0.874	0.706	0.916
LogMAR 0.3-0.6	0.770	0.720	0.604	0.470	0.716	0.596	0.823
LogMAR 0.6-1.0	0.670	0.720	0.604	0.470	0.716	0.596	0.823
LogMAR 1.0-1.3	0.630	0.585	0.502	0.333	0.521	0.413	0.702
LogMAR 1.3-1.7	0.540	0.585	0.502	0.333	0.521	0.413	0.702
CF	0.520	0.407	0.352	0.191	0.379	0.314	0.392
HM	0.350	0.407	0.352	0.191	0.379	0.314	0.392
LP	0.350	0.407	0.352	0.191	0.379	0.314	0.392

Abbreviations: CF – Counting fingers; HM – Hand motion; HUI – Health utilities index; LP – Light perception; TTO – Time-trade off; UK – United Kingdom

Deterministic scenario results applying each HRQoL source to the scenario using the EAG's proposed health states are presented in Table 26. Base case assumptions align with the new company base case (Table 15). As demonstrated, the scenario ICERs range from £19,107 to £29,407. All scenarios remain below the £30,000 threshold, however, there is a large variation in ICERs between the scenarios which suggests the assumption of combined health states is not a robust approach. In comparison, using the company's new base case, ICERs for scenarios using different utility sources only range from £14,822 (Lawrence *et al.* – HUI3) to £21,073 (Lawrence *et al.* – EQ-5D-5L) compared to the base ICER of £18,758.

Table 26. Deterministic scenario results using the EAG's proposed health states with alternative HRQoL sources (PAS price)

Parameter	Base-case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
Deterministic scenario results using the company's base case assumptions			[redacted]	[redacted]	27,053
Utility source	Brown *et al.* (1999)	Rentz *et al.* (2014)	[redacted]	[redacted]	23,233
		Lawrence *et al.* – EQ-5D-5L	[redacted]	[redacted]	28,167
		Lawrence *et al.* – HUI3	[redacted]	[redacted]	19,107
		Lawrence *et al.* – TTO	[redacted]	[redacted]	22,875
		Czoski-Murray *et al.*	[redacted]	[redacted]	29,407

Abbreviations: HUI – Health utilities index; ICER – Incremental cost-effectiveness ratio; QALYs – Quality-adjusted life-years; TTO – Time-trade off; UK – United Kingdom

B11. The EAG considers that a disutility associated with caregiver HRQoL should not be applied to patients who are in residential care as these patients will already be receiving care. As such, please update the revised base case so that carer disutility is not applied to patients assumed to be in residential care.

As detailed in Section B.1.3 of the CS, LHON has a detrimental effect on the QoL of caregivers, impacting activities of daily living, emotional functioning, relationships, work, recreation and finances.(64) Furthermore, UK clinical experts consulted by the company highlighted that older patients would require caregiver support every day.

However, the company acknowledges that a caregiver disutility may not be applied to patients who are in residential care as these patients will already be receiving care.

As such, the company have updated the economic model so that carer disutility is not applied to the proportion of patients who assumed to be in residential care.

Given that residential care is only applied to a small proportion of patients in each health state, 0%, 2%, 7%, 7%, 8%, 20%, 22% and 35%, respectively, over the age of 65 years, this update has led to a £63 minimal increase in the CS base case ICER from £20,307 to £20,370. The new company base case is detailed in Table 15.

B12. The EAG is aware of a published mapping tool developed to map from best corrected visual acuity (BCVA) to EQ-5D (Pennington *et al.* 2020. Mapping From Visual Acuity to EQ-5D, EQ-5D With Vision Bolt-On, and VFQ-UI in Patients With Macular Edema in the LEAVO Trial. *Value in Health*. 2020; 23(7):928–935). Please clarify if this tool was considered by the company to use directly reported patient data from the clinical trial as opposed to the utility values used in the model and if so, why was it not used? Please provide a scenario in the model that utilises the results of the mapping tool using directly reported patient outcomes from the clinical trial

Similar to numerous other previous NICE TAs in various eye conditions, including HST11, TA283 and TA298, utility values included in this economic analysis were derived from published literature. Whilst TA294 originally used EQ-5D to derive utility values in the base case, the assessing ERG later suggested that utilities derived from Brown *et al.* (1999) were more appropriate due to the better-seeing eye model.

Furthermore, as detailed in the CS, deriving utility values using EQ-5D was considered implausible due to the poor convergence utility when used in visual disorders. Additionally, DSU TSD 8 (‘An introduction to the measurement and valuation of health for nice submissions‘; Section 3.5), states that EQ-5D is not appropriate for assessing the impact on some forms of visual impairment, based on evidence from literature,.(65,66)

The mapping tool detailed in Pennington *et al.* 2020 was not considered by the company to derive HRQoL data from RHODOS.(67) Upon review of the analysis conducted by Pennington *et al.* 2020, the publication states that it is unclear whether the mapping analyses could be applied in visual disorders other than macular oedema secondary to central retinal vein occlusion (CRVO). This suggests this mapping tool is

not an appropriate method for deriving utility values from the clinical data for this appraisal and therefore, the company have not explored this as a scenario. Furthermore, as far as the company is aware, the VF-14 used to collect HRQOL data in RHODOS is not the same method as the VFQ-UI detailed in Pennington *et al.* and therefore, the mapping tool would not be relevant regardless.(68)

However, the company would like to highlight that in order to assess the full impact of the utility values in the economic model, the company have explored the base case utility values in the deterministic and probabilistic sensitivity analyses as well as applying values from multiple published sources (Brown *et al.* (1999), Lawrence *et al.* (2023), Czoski-Murray *et al.* (2013), Rentz *et al.* (2014)) as part of the scenario analysis. Given the varying ranges of the utility values throughout different sources, the ICER remains similar to the CS base case and do not have a substantial impact. Therefore, the company anticipate that a scenario utilising the results of the mapping tool detailed in Pennington *et al.* 2020 would also have a minimal impact on the ICER.

B13. The company applies a carer disutility to all patients in the economic model with a logMAR>1 and this is applied for the duration of the patient's lifetime. Please can the company discuss the range of care that is expected to be provided by a carer for people with varying levels of sight impairment and the duration of care that would be expected to be provided? For example, is there evidence that all patients with logMAR>1 require a carer?

LHON is a debilitating condition which significantly impacts patients' quality of life, causing significant disruption to their education, careers, and family life.(61,64,69,70)

Patients with LHON will often require full time support and require assistance with activities of daily living including shopping, climbing steps, paperwork, travel, housework, preparing meals and taking medications.(64,71,72) The number of hours spent caring for visually impaired individuals increases with severity of impairment. Insights from UK clinical experts tells us that all LHON patients will require daily informal caregiver support.(56)

Brézin et al 2005 conducted a nationwide survey of French citizens to determine the associated burden of blindness, low vision and visual impairment.(72) Overall subjects

with blindness (logMAR>1) had great difficulty in performing daily activities with 100% of subjects requiring support with shopping and paperwork, 87% with travel, 78% with housework, and 71% with preparing a meal. A 2013 systematic review of the economic burden of blindness also found that time spent by caregivers ranged from 5.8 h/ week for a person with a visual acuity of >20/32 (>0.2 LogMAR) up to 94.1 h/week and costs of for persons with a visual acuity of ≤20/250 (≤1.1 LogMAR).(73)

Overall, we consider it reasonable to assume that all LHON patients require a caregiver, with the level of care provided increasing as severity of visual impairment increases, in line with clinician opinion and published literature.

Costs and Resource Use

B14. Priority question. Due to the uncertainty in the long term effects of idebenone, the EAG's clinical experts considered that they may continue to treat patients up to three years and beyond if patients were responding to treatment or had only recently stabilised. In addition, in the CS it states that within the EAP study, treatment duration ranged from 2.4 – 70.4 months. Therefore, as a scenario, please extrapolate the persistence data using parametric curves in Figure 21 in the CS used to inform treatment costs for idebenone patients and apply the best fitting model to determine treatment costs.

The company strongly consider a scenario extrapolating the persistence data using parametric curves to be highly inappropriate and uncertain due to the low patient numbers included in the long-term follow up data beyond 36 months.

Whilst the company note that the idebenone treatment duration for the efficacy population in the EAP study ranged from 2.4 - 70.4 months, the mean treatment duration was 25.6 months and the median treatment duration was 23.2 months.

Since the EAP study is of retrospective, non-controlled and open-label nature, there is a non-uniform duration of treatment and treatment duration is left to the discretion of the treating physician. Due to this, the number of patients on treatment in the later time points (> 24months) is low. For example, in the efficacy population, the proportion of patients still on treatment at 24 months is 48% (N=42), this is substantially reduced

to nearly half of that by 36 months (26%; N=23) and only 12 patients are still receiving treatment at month 42.

Furthermore, clinical benefit in the idebenone arm is only measured up until 36 months in the CEA so extrapolating persistence data beyond this timepoint means patients are accruing additional treatment costs without experiencing any clinical benefit. This is highly biased against idebenone. As detailed in the CS, extrapolating the clinical data beyond 36 months is not clinically appropriate given the low the number of recorded observations at later time points. For example, only 11 patients provide a month 36 observation.

Additionally, UK clinical expert opinion is that patients should be treated with idebenone for one year to measure response, and then a further two years until VA stabilises. This means that some patients may complete duration before 36 months. If it is assumed that a small proportion of patients do extend treatment beyond three years, these higher costs being accrued by patients will likely be balanced out by those patients who have a shorter treatment duration.

Therefore, the company strongly consider that the persistence data should not be extrapolated beyond 36 months in order to accurately model the costs of idebenone in UK clinical practice and have not presented this as a scenario.

B15. Please provide the exact costs taken from Meads *et al.* 2003 alongside the inflated costs used in the economic model and clarify the specific inflation index that was used.

The costs taken from the Meads et al. 2003 publication can be found in Table 2 of the publication and the specific costs used in the CS can be found in Table 27. To inflate the costs from cost year 2001 to 2022 the company used PSSRU HCHS pay and price indices.(74) From this, the inflation factor1.69 was derived.

Table 27. Meads et al. 2003 inflated costs

Name of cost in model	Name and cost used from publication	Inflation factor	Cost in model
Outpatient care	Low vision aids: £136.33 Low vision rehabilitation: £205.30	1.69	Outpatient care: £577.26
Community care - Blind registration	Blind registration: £59.70 + £37.71		Community care - Blind registration: £164.74
Community care - supportive living	Community care: £2,848.63		Community care - supportive living: £4,818.23
Residential care	Residential care: £15,904.41		Residential care: £26,896.83
Depression resulting from LHON	Depression: £391.97		Depression resulting from LHON: £662.90

Abbreviations: LHON – Leber's hereditary optic neuropathy

B16. The EAG notes considerable uncertainty with the resource use applied for health state costs and the differences applied across the health states.

a) **Clinical experts to the EAG suggested that there would be no additional costs of blind registration outside of that covered in an ophthalmology visit. Please clarify why separate costs are applied for blind registration? In addition please clarify why a proportion of patients who would not be classed as sight impaired (logMAR <1) still have the cost of blind registration (certification of sight impairment) applied?**

The company have found no evidence that the cost of blind registration is included in the cost of an ophthalmology visit. According to information pages from The Royal National Institute of Blind People (RNIB) and the NHS, an ophthalmologist specialist will only determine if a patient can be certified partially sighted or blind. The patient can then register blind separately and it is not compulsory for a patient to do so.(75,76)

Furthermore, the proportion of patients who have the cost of blind registration applied across health states are informed by KOLs in ophthalmology further validated by UK clinical experts. Whilst 100% of patients with LogMAR>1 have a cost of blind registration applied, it is assumed that a small proportion of patients with LogMAR <1

accrue a blind registration cost. On the other hand, all patients are expected to attend ophthalmology visits across all VA health states.

Therefore, the company maintain that blind registration costs should be applied separate to the cost of an ophthalmology visit.

b) **Meads *et al.* 2003, which informed the resources included in the economic model, only listed costs related to hospitalisation due to hip replacement and the proportion of blind people who require hip replacement was estimated from studies of visual difficulties of people in retirement homes (estimated as 5% of patients only). Therefore, hospitalisation costs only seem applicable to older patients and to a small proportion of patients as opposed to a regular cost. Therefore, based on the evidence available, please clarify why costs of hospitalisation are applied regularly (every three months) for a patient's lifetime and do not follow the resource use provided in Meads *et al*.?**

The cost of hospitalisation in the company's CEA is sourced from the NHS reference costs based on the cost of A&E attendance, not Meads *et al*.(77) KOLs in ophthalmology were generally aligned on the proportion of patients who accrue hospitalisation costs which the survey defines as the proportion of patients who required care due to injurious falls. The inputs are also further validated by UK clinical experts.

The company highlight that Meads *et* al. is a study exploring a cohort of elderly people and therefore only listed costs related to hospitalisation due to hip replacements informed by a population of people in retirement homes. However, literature has demonstrated that falls due to partial sightedness and blindness can occur in all ages. The Royal National Institute of Blind People (RNIB) conducted research into estimating the number of falls due to partial sightedness and blindness in the UK using the methodology from Scuffham *et al.* (2002).(78) The report estimated that around 8,021 falls related to partial sightedness and blindness occurred in patients aged 18-59 in 2008, consisting of admitted, A&E, day cases, and ambulance fall types. The

study also reports that half of fallers fall recurrently, which supports the regular application of hospitalisation costs.

Nevertheless, the proportion of patients with hospitalisation costs applied to the company's CEA remains low across each health state (2%, 3%, 10%, 18%, 20%, 22%, 27% and 30% for each health state, respectively). The company therefore maintain that hospitalisation costs should be applied regularly to patients of all ages with varying VA.

c) **The company's model applies regular per cycle costs for outpatient care, deemed to consist of low vision aids and rehabilitation services. Clinical experts suggested to the EAG that supplying low vision aids, in the form of magnification tools and rehabilitation would not be an ongoing regular cost throughout a patient's lifetime but more an one off cost required on sight deterioration (likely when considered sight impaired [logMAR>1]). Therefore, the EAG deems it more likely that these services would be provided as a one-off cost rather than a per cycle cost. Please provide a scenario to reflect this.**

The company have conducted a scenario exploring the impact of applying the outpatient care cost as a one-off cost to patients across all health states.

The deterministic scenario results applying a one-off outpatient care cost for idebenone vs SoC are presented in Table 28. The scenario is applied to the new company base case detailed in Table 15. The scenario presents a minimal increase in the ICER of £837, from £18,758 to £19,595.

Table 28: Deterministic scenario results applying outpatient care as a one-off cost (PAS price)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
SoC	[redacted]	[redacted]	[redacted]	[redacted]	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	19,595

Abbreviations: ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life-years; SoC – Standard of care

d) Please provide a scenario which uses the proportions of patients for each resource use reported directly in Meads *et al*. applied to patients in all health states in which patients are classed as blind (logMAR>1) as opposed to proportions estimated by clinical experts used in the base case.

The company would like to highlight that the proportion of patients expected to uptake each resource use informed by KOLs and validated by UK clinical experts are more appropriately aligned with anticipated resource use in UK clinical practice and provide more up to date estimations compared to the estimations in Meads *et al.*(79) Furthermore, the proportions of patients using each resource use reported in Meads *et al.* are based on an elderly population who are strictly classed as blind which does not align with the population in this CEA, with a mean age of 34 years and VA ranging from perfect sight to LP.(79)

Furthermore, it is not appropriate to assume that only patients with LogMAR > 1 accrue resource use costs. For example, as highlighted in the report conducted by RNIB above, falls occur in patients with partial sightedness as well as full blindness which suggest that patients in the better LogMAR health states will still accrue hospitalisation costs.(75) Additionally, Brown *et al.* demonstrated a substantial decrease in patient QoL across the perfect vision to LogMAR = 1 VA categories (0.92 in LogMAR =0 to 0.67 in LogMAR = 1) which shows considerable limitations in patients' ability to function in daily life and activities of employment as their VA worsens.(54) This will translate to an increased resource use uptake in patients with <0.3 LogMAR <1 as assumed in the CEA.

The company have conducted a scenario which explores the impact of applying the proportion of patients who use each resource use reported directly in Meads *et al.* for patients with LogMAR>1.(79) Since hospitalisation costs modelled in this CEA are based on patients who experience injurious falls and not patients who undergo a hip replacement, the proportion of patients who accrue hospitalisation costs remain aligned with the KOL survey. Furthermore, since it is not clinically appropriate to assume that all patients with LogMAR < 1 do not accrue resource use cost across the time horizon of the model, the proportion of patients who use each resource use in the

LogMAR < 1 health states also remain aligned with the KOL survey. The proportion of patients using each resource applied in this scenario are presented in Table 29.

Table 29: Resource use adjusted for inputs from Meads et al.(79)

Resource	LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6-1.0	LogMAR 1.0-1.3	LogMAR 1.3-1.7	CF	HM	LP
Hospitalisation	2%	3%	10%	18%	20%	22%	27%	30%
Outpatient care	13%	38%	80%	22%	22%	22%	22%	22%
Community care - Blind registration	0%	25%	78%	95%	95%	95%	95%	95%
Community care - supportive living	0%	0%	20%	6%	6%	6%	6%	6%
Residential care	0%	2%	7%	30%	30%	30%	30%	30%
Depression resulting from LHON	7%	20%	30%	39%	39%	39%	39%	39%

Abbreviations: CF – Counting fingers; HM – Hand motion; LHON – Leber's hereditary optic neuropathy; LP – Light perception

The deterministic scenario results applying the adjusted resource use inputs for idebenone vs SoC are presented in Table 30. The scenario is applied to the new company base case detailed in Table 15. The scenario presents a minimal increase in the ICER of £3,520, from £18,758 to £22,277, as this scenario underestimates resource use across heath states and therefore underestimates savings obtained with idebenone treatment.

Table 30: Deterministic scenario results applying the adjusted resource use inputs based on Meads et al. (PAS price)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
SoC	[redacted]	[redacted]	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	22,277

Abbreviations: ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life-years; SoC – Standard of care

B17. The EAG notes that a cost for residential care for people aged >65 is available directly from PSSRU 2022 and therefore should be used rather than inflating costs from Mead *et al*. Please update the model to use the lease cost of residential care using the local authority own-provision residential care for older people (age 65+) unit cost from the PSSRU (Section 1.3) (£1,442 per week) in a revised base case

The company would like to thank the EAG for highlighting this more recent cost for residential care from PSSRU 2022. The company have therefore updated the cost of residential care to £1,442 per week in the economic model which translates to an annual cost of £75,242 (compared to an annual cost £26,897 previously used in the CEA based on Meads *et al.*).

This has led to a £3,441 decrease in the CS base case ICER from £20,307 to £16,866. The new company base case is detailed in Table 15.

B18. The cost used for ophthalmology visit uses NHS Reference cost for "Ophthalmology service, Non-Admitted Face-to-Face Attendance, Follow-up". An additional unit cost is available to represent first visit (Non-Admitted Face-to-Face

Attendance, First, £166.64). Please amend the model to appropriately apply separate costs for initial and subsequent ophthalmology visits.

The company would like to thank the EAG for highlighting that there is an NHS reference cost for the first ophthalmology visit. The company have applied a cost of £166.64 ("Ophthalmology service, Non-Admitted Face-to-Face Attendance, First") to the first ophthalmology visit for each patient in the model (compared to a cost of £144 previously used in the CEA).(77)

This has led to a negligible increase of £3 in the CS base case ICER from £20,307 to £20,310. The new company base case is detailed in Table 15.

B19. One of the company's clinical experts (reported in Appendix N) noted how a one-off liver function test may be required for patients treated with idebenone. In addition, clinical experts to the EAG stated that patients with LHON would have optical coherence tomography (OCT) undertaken each time they had an outpatient visit. Please provide a scenario which includes both of these costs.

The company acknowledge that one-off liver function test may be required for patients treated with idebenone, based on clinical expert opinion. The company assume that a one-off liver function test would be costed as a blood test, sourced from the NHS reference costs as 'Haematology, Directly Accessed Pathology Services' (DAPS05), which assumes a cost of £2.96. Given such a small cost in comparison to the total costs per treatment arm, the company anticipate this change would have a negligible impact on the ICER and therefore have not included this update in the model.

The company have, however, applied a cost of OCT for each ophthalmology visit. The cost was sourced from the NHS reference costs and assumed to be the cost of 'Retinal Tomography, 19 years and over' (BZ88A), which assumes a cost of £158.23.

This has led to a £96 minimal increase in the CS base case ICER from £20,307 to £20,403. The new company base case is detailed in Table 15.

B20. Please clarify how regularly Idebenone will be prescribed in clinical practice, i.e would it be a monthly prescription or every three months?

Idebenone would typically be prescribed through standard NHS procedures for high-cost drugs, typically of 3 months at a time. There is no requirement for cold-chain or any special requirements.

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Appendix 1

Table 31: Re-examination of studies originally rejected for "Intervention" in the RWE SLR

S.no.	Publication Source	First author	Title	Selection	Reason for rejection	Explanation
19	Investigative ophthalmology & visual science. 63(1) (pp 43), 2022.	Calzetti G.	Longitudinal Study of Optic Disk Perfusion and Retinal Structure in Leber's Hereditary Optic Neuropathy.	NO	Intervention	Non-interventional study examining optic disk perfusion and neural retinal structure in LHON carriers and healthy controls
36	Documenta Ophthalmologica. (no pagination), 2015.	Jarc-Vidmar M.	Clinical and electrophysiology findings in Slovene patients with Leber hereditary optic neuropathy.	NO	Intervention	Non-interventional case series reporting clinical and electrophysiology findings in 8 Slovene patients.
87	Orphanet Journal of Rare Diseases. 16(1) (no pagination), 2021. Article Number: 127.	Rabenstein A.	Smoking and alcohol, health-related quality of life and psychiatric comorbidities in Leber's Hereditary Optic Neuropathy mutation carriers: a prospective cohort study.	NO	Intervention	Cross-sectional analysis reporting smoking and alcohol, health-related quality of life and psychiatric comorbidities in LHON, without treatment subgroup data.
92	British Journal of Ophthalmology. 105(8) (pp 1166-1171), 2021.	Wang D.	Characterisation of thickness changes in the peripapillary retinal nerve fibre layer in patients with Leber's hereditary optic neuropathy.	NO	Intervention	Cross-sectional study comparing peripapillary retinal nerve fibre layer between LHON patients and health controls. Treatment not mentioned.
107	Molecular Genetics and Metabolism Reports. 27 (no pagination), 2021. Article Number: 100733.	Loos M.A.	Clinical and molecular characterization of mitochondrial DNA disorders in a group of Argentinian pediatric patients.	NO	Intervention	Non-interventional study describing clinical features and molecular characterization of patients with mitochondrial DNA disorders.
108	NeuroImage: Clinical. 30 (no pagination), 2021. Article Number: 102619.	Zhang J.	Abnormal large-scale structural rich club organization in Leber's hereditary optic neuropathy.	NO	Intervention	Non-interventional study investigating large-scale structural rich club organization in LHON.
110	Journal of neuro-ophthalmology : the official journal of the North American Neuro-Ophthalmology Society. 40(1) (pp 30-36), 2020.	Cui S.	Clinical Features of Chinese Sporadic Leber Hereditary Optic Neuropathy Caused by Rare Primary mtDNA Mutations.	NO	Intervention	Characterization of Chinese patients with sporadic Leber hereditary optic neuropathy (LHON) caused by rare primary mitochondrial DNA mutations. No treatment examined.
111	Journal of neuro-ophthalmology : the official journal of the North American Neuro-Ophthalmology Society. 40(1) (pp 15-21), 2020.	Moon Y.	Clinical and Optic Disc Characteristics of Patients Showing Visual Recovery in Leber Hereditary Optic Neuropathy.	NO	Intervention	Examination of clinical and optic disc features are associated with visual recovery in patients with LHON. Patient exposure to treatment was not specified, and subgroup data not reported.
119	Eye (Basingstoke). (no pagination), 2021.	Yu-Wai-Man P	Natural history of patients with Leber hereditary optic neuropathy-results from the REALITY study.	YES		Subgroup of patients with ND4 mutation treated with idebenone reported
131	Frontiers in Neurology. 11 (no pagination), 2020.	Botelho G.I.S.	Impaired Ganglion Cell Function Objectively	NO	Intervention	Non-interventional cross-sectional study assessing ganglion cell function by photopic negative

	Article Number: 628014.		Assessed by the Photopic Negative Response in Affected and Asymptomatic Members From Brazilian Families With Leber's Hereditary Optic Neuropathy.			response in affected and asymptomatic carriers from Brazilian families with LHON.
141	Multiple Sclerosis and Related Disorders. 44 (no pagination), 2020. Article Number: 102337.	Alves J.M.	Optic neuropathy: A 15-year retrospective observational study.	NO	Intervention	Treatment not specified for the single LHON patient included in the study.
145	Graefe's Archive for Clinical and Experimental Ophthalmology. 258(10) (pp 2283-2290), 2020.	Ahn Y.J.	Genotypic and phenotypic characteristics of Korean children with childhood-onset Leber's hereditary optic neuropathy.	NO	Intervention	Non-interventional study describing genotypic and phenotypic characteristic of seventeen patients aged 13 years or younger with optic atrophy with positive mitochondrial DNA (mtDNA) demonstrating childhood-onset LHON.
163	Brain Sciences. 10(6) (pp 1-12), 2020. Article Number: 359. D	Jonak K.	Neuroanatomical changes in leber's hereditary optic neuropathy: Clinical application of 7T mri submillimeter morphometry.	NO	Intervention	Non-interventional study outlining morphometric changes in subcortical brain areas and their associations with the clinical picture in LHON.
171	Ophthalmology. 127(5) (pp 679-688), 2020.	Poincenot L.	Demographics of a Large International Population of Patients Affected by Leber's Hereditary Optic Neuropathy.	NO	Intervention	Non-interventional study describing mutation type, age of symptom onset, and gender distributions in LHON.
183	Investigative Ophthalmology and Visual Science. Conference: 2020 Annual Meeting Association for Research in Vision and Ophthalmology, ARVO 2020. Baltimore, MD United States. 61(7) (no pagination), 2020.	Berezovsky A.	Longitudinal analysis of photopic negative response in carriers and affected members of the 11778 SOA-BR Leber's hereditary optic neuropathy pedigree.	NO	Intervention	Study investigating retinal ganglion cell function by the photopic negative response (PhNR) in members from a Brazilian family. Treatment outcomes not reported.
191	Eye (Basingstoke). 34(9) (pp 1624-1630), 2020.	Darvizeh F.	Choroidal thickness and the retinal ganglion cell complex in chronic Leber's hereditary optic neuropathy: a prospective study using swept-source optical coherence tomography.	NO	Intervention	Non-interventional study measuring choroidal thickness in chronic LHON and correlating thickness changes with the retinal ganglion cell-inner plexiform layer. No treatment examined.
204	Klinische Monatsblatter fur Augenheilkunde. 236(4) (pp 451-461), 2019.	Lazdinyte S.	Analysis of Inherited Optic Neuropathies.	NO	Intervention	Non-interventional study presenting snapshot of clinical and genetic conditions - no treatment included.
206	International Ophthalmology. 39(1) (pp 155-166), 2019.	Karti O.	Baseline demographics, clinical features, and treatment protocols of 240 patients with optic neuropathy: experiences from a neuro-ophthalmological clinic in the Aegean region of Turkey.	NO	Intervention	Treatment protocols reported, associated outcomes not reported.

217	Ophthalmology. 126(7) (pp 1033-1044), 2019.	Parisi V.	Functional Changes of Retinal Ganglion Cells and Visual Pathways in Patients with Chronic Leber's Hereditary Optic Neuropathy during One Year of Follow-up.	NO	Intervention	Retrospective case series including untreated patients with chronic LHON.
218	Current Eye Research. 44(6) (pp 638-644), 2019.	Asanad S.	Optical Coherence Tomography of the Retinal Ganglion Cell Complex in Leber's Hereditary Optic Neuropathy and Dominant Optic Atrophy.	NO	Intervention	Examination of the thicknesses of the peripapillary RNFL (pRNFL) along with the macular RGC-IPL using optical coherence tomography (OCT) among acute and chronic LHON, DOA, and normal healthy control patients. No treatment specified.
219	Journal of Neuro-Ophthalmology. 39(1) (pp 56-59), 2019.	Cui S.	Evaluation of Vision-Related Quality of Life in Chinese Patients With Leber Hereditary Optic Neuropathy and the G11778A Mutation.	NO	Intervention	Assessment of QoL outcomes in LHON that does not specify treatment used
220	BMJ Open. 9(3) (no pagination), 2019. Article Number: e025307.	Liu H.-L.	What are the characteristics and progression of visual field defects in patients with Leber hereditary optic neuropathy: A prospective single-centre study in China.	NO	Intervention	Prospective study describing the characteristics and progression of visual field defects in patients with Leber hereditary optic neuropathy over 12 months. Treatments were not reported/specified.
240	Journal of Neuro-Ophthalmology. 38(3) (pp 308-311), 2018.	Dhiman R.	Neuro-ophthalmology at a tertiary eye care centre in India.	NO	Intervention	Description of the spectrum and profile of patients presenting to a tertiary eye care center with neuro-ophthalmic disorders, with no subgroup or treatment data available for LHON patients.
242	American Journal of Ophthalmology. 192 (pp 217-228), 2018.	Borrelli E.	Topographic Macular Microvascular Changes and Correlation With Visual Loss in Chronic Leber Hereditary Optic Neuropathy.	NO	Intervention	Cross-sectional study evaluating quantitative data from the macular microvascular networks in LHON eyes. No treatment examined.
249	Clinical and Experimental Ophthalmology. 46(9) (pp 1055-1062), 2018.	Balducci N.	Peripapillary vessel density changes in Leber's hereditary optic neuropathy: a new biomarker.	NO	Intervention	Cross-sectional study measuring the peripapillary capillary vessel density (VD) using optical coherence tomography angiography (OCT-A) at different stages of LHON. Patient treatment not specified.
251	Journal of Neuro-Ophthalmology. 38(4) (pp 466-469), 2018.	Orssaud C.	Cardiac Disorders in Patients with Leber Hereditary Optic Neuropathy.	NO	Intervention	Case series characterizing cardiac abnormalities in a large patient cohort with LHON. Treatment for LHON not specified.
268	Investigative Ophthalmology and Visual Science. Conference: 2018 Annual Meeting of the Association for Research in Vision and Ophthalmology, ARVO 2018. Honolulu, HI United States. 59(9) (no pagination), 2018.	Frousiakis S.	Cardiovascular comorbidity in Leber's hereditary optic neuropathy mtDNA 11778.	NO	Intervention	Chart review investigating cardiovascular comorbidity in subjects with LHON 11778 mitochondrial DNA (mtDNA) mutation. Treatments for LHON not specified.

269	Investigative Ophthalmology and Visual Science. Conference: 2018 Annual Meeting of the Association for Research in Vision and Ophthalmology, ARVO 2018. Honolulu, HI United States. 59(9) (no pagination), 2018.	Silva M.	Natural History Data (NHD) In A Cohort Of 383 Patients with Leber's Hereditary Optic Neuropathy (LHON). Results From An International Retrospective Case Record Survey (CRS).	NO	Outcomes	No outcomes reported - only genotype, sex, and LHON presentation reported.
275	Investigative Ophthalmology and Visual Science. Conference: 2018 Annual Meeting of the Association for Research in Vision and Ophthalmology, ARVO 2018. Honolulu, HI United States. 59(9) (no pagination), 2018.	Pajic S.P.	Genotype and phenotype characteristics of leber hereditary optic neuropathy (LHON) patients in slovenia.	NO	Intervention	Non-interventional study reporting genotype and phenotype characteristics in Slovene LHON patients.
281	Acta Ophthalmologica. Conference: 2018 European Association for Vision and Eye Research Conference, EVER 2018. Nice France. 96(Supplement 261) (pp 117), 2018.	Silva M.	Natural history findings from a large cohort of patients with leber's hereditary optic neuropathy (LHON): New insights into the natural disease-course.	NO	Intervention	Treatment details or associated outcomes not reported.
284	Journal of Inherited Metabolic Disease. Conference: 56th Annual Symposium of the Society for the Study of Inborn Errors of Metabolism, SSIEM 2018. Athens Greece. 41(Supplement 1) (pp S151-S152), 2018.	Keshavan N.	Natural history of mitochondrial disorders: A systematic review.	NO	Study design	SLR abstract
285	Journal of Inherited Metabolic Disease. Conference: 56th Annual Symposium of the Society for the Study of Inborn Errors of Metabolism, SSIEM 2018. Athens Greece. 41(Supplement 1) (pp S160), 2018.	Kolarova H.	Extraocular features in 414 German and Czech individuals with Leber hereditary optic neuropathy.	NO	Intervention	Non-interventional study examining the prevalence of extraocular symptoms in LHON.
287	European Journal of Neurology. Conference: 4th Congress of the European Academy of Neurology, EAN 2018. Lisbon Portugal. 25(Supplement 2) (pp 341), 2018.	Catarino C.	Quality of life and modifiable lifestyle factors in Leber's Hereditary Optic Neuropathy mutation carriers.	NO	Intervention	Non-interventional study describing QoL in LHON-carriers
289	European Journal of Neurology. Conference: 4th Congress of the European Academy of Neurology, EAN 2018. Lisbon	Radelfahr F.	Higher relative proportion of Leber's Hereditary Optic Neuropathy in premenarchal and postmenopausal women supports a	NO	Intervention	Examination of women's reproductive age (menarche, childbearing age, menopause) and LHON onset. No treatment mentioned or examined.

	Portugal. 25(Supplement 2) (pp 265), 2018.		protective role of estrogens.			
291	Documenta Ophthalmologica. Conference: 56th Annual Symposium of the International Society for Clinical Electrophysiology of Vision, ISCEV 2018. Reims France. 136(Supplement 1) (pp 49-50), 2018.	Arndt C.	Visual evoked potentials in patients with inherited optic neuropathy.	NO	Intervention	Case series examining visual evoked potential (VEP) responses to evaluate optic nerve function in LHON. No treatment examined.
305	Mitochondrion. 36 (pp 138-149), 2017.	Majander A.	The pattern of retinal ganglion cell dysfunction in Leber hereditary optic neuropathy.	NO	Intervention	Case series describing pattern of retinal ganglion cell dysfunction. Treatment not specified.
314	Psychosomatics. 58(1) (pp 38-45), 2017. Date of Publication: 01 Jan 2017.	Gale J.	An International Study of Emotional Response to Bilateral Vision Loss Using a Novel Graphical Online Assessment Tool.	NO	Intervention	Survey results reporting on the emotional aspects rapid bilateral blindness. Use of treatments not mentioned
315	Ophthalmology. 124(6) (pp 843-850), 2017.	Hwang T.J.	Natural History of Conversion of Leber's Hereditary Optic Neuropathy: A Prospective Case Series.	NO	Study design	Case series
316	Investigative Ophthalmology and Visual Science. 58(11) (pp 4586-4592), 2017.	Vestergaard N.	Increased mortality and comorbidity associated with leber's hereditary optic neuropathy: A nationwide cohort study.	NO	Intervention	Health registry analysis reporting incidence of comorbidities and mortality for patients with LHON and unaffected family members was compared with that in the general population. Treatment use not mentioned.
323	British Journal of Ophthalmology. 101(11) (pp 1505-1509), 2017..	Majander A..	Childhood-onset Leber hereditary optic neuropathy.	NO	Intervention	Description of the clinical and molecular genetic features associated with Childhood-onset LHON (visual loss occurred at the age of 12 years or younger with a confirmed pathogenic mitochondrial DNA mutation). Treatment given to patients not reported.
328	Investigative Ophthalmology and Visual Science. Conference: 2017 Annual Meeting of the Association for Research in Vision and Ophthalmology, ARVO 2017. Baltimore, MD United States. 58(8) (no pagination), 2017.	Parisi V.	Visual function changes in patients with Leber's hereditary optic neuropathy during one year of follow-up.	NO	Intervention	Assessment of changes in retinal ganglion cell (RGC) and visual pathways function in patients with Leber's hereditary optic neuropathy (LHON) during one year of follow-up. Treatment given to patients not reported.
337	Documenta Ophthalmologica. Conference: 55th Annual Symposium of the International Society for Clinical Electrophysiology of Vision, ISCEV 2017. Miami, FL United States. 135(1 Supplement 1) (pp 22-23), 2017.	Coupland S.G.	The photopic negative response: An objective measure of retinal ganglion cell function in patients with leber's hereditary optic neuropathy.	NO	Intervention	Evaluation of PhNR as an objective non-invasive clinical metric in LHON. Treatment details not reported.
338	Documenta Ophthalmologica.	Wang M.	Electrophysiological and structural retinal	NO	Intervention	Clinical and electrophysiological findings in 15 Chinese patients with

	Conference: 55th Annual Symposium of the International Society for Clinical Electrophysiology of Vision, ISCEV 2017. Miami, FL United States. 135(1 Supplement 1) (pp 37), 2017.		changes in chinese patients with leber hereditary optic neuropathy.			LHON. Treatment details not reported.
342	Acta Ophthalmologica. Conference: 22nd European Association for Vision and Eye Research Conference, EVER 2017. Nice France. 95(Supplement 259) (no pagination), 2017.	Liu H.	Differences in onset between eyes in patients with Leber's hereditary optic neuropathy (LHON).	NO	Intervention	Comparison of the age of disease onset and time interval between affected eyes by mutation in LHON patients. Treatment details not reported.
350	Neuro-Ophthalmology. Conference: 13th Meeting of the European Neuro-Ophthalmological Society, EUNOS 2017. Budapest Hungary. 41(Supplement 1) (pp S40-S41), 2017.	Celebisoy N.	Baseline demographics, clinical features and treatment protocols of 240 patients with optic neuropathy: Experiences from a neuro-ophthalmology clinic in the aegean region of turkey.	NO	Intervention	Treatment protocols reported, associated outcomes not reported.
357	Journal of epidemiology. 27(9) (pp 447-450), 2017.	Ueda K.	Nationwide epidemiological survey of Leber hereditary optic neuropathy in Japan.	NO	Intervention	Nationwide survey to estimate the annual incidence of LHON cases with molecular confirmation in Japan. Treatments and associated outcomes not reported.
365	Investigative Ophthalmology and Visual Science. 57(8) (pp 3872-3883), 2016.	Moster S.J.	Retinal ganglion cell and inner plexiform layer loss correlate with visual acuity loss in LHON: A longitudinal, segmentation OCT analysis.	NO	Intervention	Description of longitudinal retinal changes in LHON. Treatments received and associated outcomes not reported.
374	Ophthalmic Surgery Lasers and Imaging Retina. 47(9) (pp 802-810), 2016.	Lam B.L.	Macular retinal sublayer thicknesses in G11778A leber hereditary optic neuropathy.	NO	Intervention	Comparison of retinal sublayer thickness in LHON patients and healthy controls. No treatment details reported.
381	Neuromuscular Disorders. 26(4-5) (pp 272-276), 2016.	Mancuso M.	"Mitochondrial neuropathies": A survey from the large cohort of the Italian Network.	NO	Intervention	Examination of neuropathy in mitochondrial diseases. Treatment details/outcomes associated with LHON patients not reported.
393	Investigative Ophthalmology and Visual Science. Conference: 2016 Annual Meeting of the Association for Research in Vision and Ophthalmology, ARVO 2016. Seattle, WA United States. 57(12) (pp 5074), 2016.	Frousiakis S.E.	Ganglion cell complex thickness in mitochondrial Optic neuropathies.	NO	Intervention	Examination of ganglion cell complex (GCC) across mitochondrial optic neuropathies. Treatment details not reported.
410	Scientific reports. 6 (pp 37332), 2016.	Borrelli E.	Changes in Choroidal Thickness follow the RNFL Changes in Leber's	NO	Intervention	Quantitative assessment of choroidal thickness in LHON, as compared to controls and DOA. No report of treatment details.

			Hereditary Optic Neuropathy.			
434	Investigative Ophthalmology and Visual Science. Conference: 2015 Annual Meeting of the Association for Research in Vision and Ophthalmology, ARVO 2015. Denver, CO United States. 56(7) (pp 3860), 2015.	Ammar M.	Functional visual outcome of 1st vs 2nd affected eye in treated Ihon patients at 1 year.	YES		Reports outcomes for quinone therapy (probably refers to idebenone but that is not clearly stated)
463	European Journal of Paediatric Neurology. 18(3) (pp 354-359), 2014.	Jancic J.	Leber hereditary optic neuropathy in the population of Serbia.	NO	Intervention	Population-based clinical and molecular-genetic study of LHON in the Serbian population. Treatment details/outcomes not reported.
471	Experimental and Therapeutic Medicine. 7(2) (pp 483-487), 2014.	Zhang Y.	Characterization of retinal nerve fiber layer thickness changes associated with leber's hereditary optic neuropathy by optical coherence tomography.	NO	Intervention	Characterization of retinal nerve fiber layer thickness changes associated. Treatment details/outcomes not reported.
473	JAMA Ophthalmology. 132(4) (pp 428-436), 2014.	Lam B.L.	Trial end points and natural history in patients with G11778A leber hereditary optic neuropathy: Preparation for gene therapy clinical trial.	YES		Previously captured only as a bibliographic reference. PRISMA updated to reflect this.
486	Investigative Ophthalmology and Visual Science. Conference: 2014 Annual Meeting of the Association for Research in Vision and Ophthalmology, ARVO 2014. Orlando, FL United States. 55(13) (pp 1885), 2014.	Frousiakis S.E	Cardiac conduction in leber's hereditary optic neuropathy.	NO	Intervention	Evaluation of cardiac conduction in LHON patients and carriers. No treatment examined.
487	Investigative Ophthalmology and Visual Science. Conference: 2014 Annual Meeting of the Association for Research in Vision and Ophthalmology, ARVO 2014. Orlando, FL United States. 55(13) (pp 1884), 2014.	Parisi V.	Multifocal bioelectrical cortical responses in leber hereditary optic neuropathy.	NO	Intervention	Examination of visual cortical bioelectrical responses in LHON and control eyes. Treatment details not reported.
488	Investigative Ophthalmology and Visual Science. Conference: 2014 Annual Meeting of the Association for Research in Vision and Ophthalmology, ARVO 2014. Orlando, FL United States. 55(13) (pp 1882), 2014.	Pouw A.	Perimetric parameters in unaffected carriers of Leber's Hereditary Optic Neuropathy (LHON).	NO	Intervention	Evaluation of Humphrey Visual Fields (HVF) for subclinical changes among untreated LHON carriers.
502	BMC ophthalmology. 14 (pp 105), 2014.	Zhang Y.	Characterization of macular thickness	NO	Intervention	Characterization of macular thickness (MT) changes in LHON,

			changes in Leber's hereditary optic neuropathy by optical coherence tomography.			compared to controls. No treatment details reported.
513	Brain. 136(11) (pp 3418-3426), 2013..	Kisimbi J.	Macular spectral domain optical coherence tomography findings in Tanzanian endemic optic neuropathy.	NO	Intervention	No treatment details reported for LHON subgroup.
515	Journal of Neuro-Ophthalmology. 33(4) (pp 349-353), 2013.	Altpeter E.K.	Evaluation of fixation pattern and reading ability in patients with leber hereditary optic neuropathy.	NO	Intervention	Evaluation of fixation pattern and reading ability in LHON. Treatment details or associated outcomes not reported.
523	Investigative Ophthalmology and Visual Science. Conference: 2013 Annual Meeting of the Association for Research in Vision and Ophthalmology, ARVO 2013. Seattle, WA United States. 54(15) (no pagination), 2013.	Wolff B.	Inner nuclear layer microcystic changes in optic nerve atrophy: A prospective study.	NO	Intervention	Treatment details or associated outcomes not reported.
539	Neuro-Ophthalmology. Conference: 11th European Neuro-Ophthalmology Society, EUNOS Meeting. Oxford United Kingdom. Conference Publication: (var.pagings). 37(SUPPL. 1) (pp 37), 2013.	Zhang Y.X.	Macular thickness reduction in unaffected female carriers with leber hereditary optic neuropathy by optical coherence tomography.	NO	Intervention	Examination of macular thickness reduction in untreated LHON female carriers.
540	Neuro-Ophthalmology. Conference: 11th European Neuro-Ophthalmology Society, EUNOS Meeting. Oxford United Kingdom. Conference Publication: (var.pagings). 37(SUPPL. 1) (pp 37), 2013..	Zhang Y.X.	Macular thickness evaluation by spectral domain optical coherence tomography in leber hereditary optic neuropathy.	NO	Intervention	Examination of macular thickness reduction in LHON, compared to control. No treatment examined.
549	Investigative ophthalmology & visual science. 54(10) (pp 6893-6901), 2013.	Ziccardi L.	Retinal function and neural conduction along the visual pathways in affected and unaffected carriers with Leber's hereditary optic neuropathy.	NO	Intervention	Examination of retinal function and neural conduction along the visual pathways in affected and unaffected carriers with LHON, as well as normal subjects. No treatment details reported.
566	Clinical Neuropathology. Conference: 10th European Congress of Neuropathology. Edinburgh United Kingdom. Conference Publication: (var.pagings). 31(4) (pp 321), 2012.	Pal E.	Mitochondrial diseases: Clinico-pathological correlations.	NO	Intervention	Treatments details not reported for LHON subgroup

581	Neuro-Ophthalmology. Conference: 19th Biennial Meeting of the International Neuro-Ophthalmology Society, INOS 2012. Singapore. Conference Publication: (var.pagings). 36(SUPPL. 1) (pp 10), 2012.	Orssaud C.	Stability of visual function after recovery in leber hereditary optic neuropathy.	NO	Intervention	Examination of visual function after LHON patients experienced a spontaneous or therapy-induced visual recovery. Mixed population with no intervention specified or subgroup data of outcomes available.
584	Journal of Neurology. 259(3) (pp 542-550), 2012.	Rance G.	Auditory function in individuals within Leber's hereditary optic neuropathy pedigrees.	NO	Intervention	Examination of auditory dysfunction in LHON. No treatment details reported.
593	Investigative Ophthalmology and Visual Science. 52(7) (pp 4742-4748), 2011.	Kaewsutthi S.	Mitochondrial haplogroup background may influence Southeast Asian G11778A leber hereditary optic neuropathy.	NO	Intervention	Investigation of the role of mitochondrial DNA (mt DNA) background on the expression of Leber hereditary optic neuropathy. No treatment details reported.
624	Ophthalmology. 117(3) (pp 623-627), 2010.	Barboni P.	Natural History of Leber's Hereditary Optic Neuropathy: Longitudinal Analysis of the Retinal Nerve Fiber Layer by Optical Coherence Tomography.	NO	Intervention	Examination of the topographic pattern and temporal sequence of fiber loss in the peripapillary retinal nerve fiber layer in 4 LHON patients. No interventions examined.
629	British Journal of Ophthalmology. 94(1) (pp 121-127), 2010.	Gronlund M.A.	Ophthalmological findings in children and young adults with genetically verified mitochondrial disease.	NO	Intervention	Description of ophthalmological phenotypes in young adults with LHON. No treatment details reported.
654	Neuro-Ophthalmology. 31(5-6) (pp 207-210), 2007.	Wang W.	Clinical features of genetically proved Leber hereditary optic neuropathy in China.	NO	Intervention	Treatment details or associated outcomes were not reported in the conference paper.
666	American Journal of Ophthalmology. 141(4) (pp 676-682.e1), 2006.	Spruijt L.	Influence of mutation type on clinical expression of leber hereditary optic neuropathy.	NO	Intervention	Comparison of mutation type on clinical expression of LHON. Treatment details were not reported.
670	Ophthalmology. 112(1) (pp 120-126), 2005.	Barboni P.	Retinal nerve fiber layer evaluation by optical coherence tomography in Leber's hereditary optic neuropathy.	NO	Intervention	Cross-sectional study evaluating retinal nerve fiber layer in LHON. No treatment details reported.
671	Ophthalmology. 112(1) (pp 127-131), 2005.	Savini G.	Retinal nerve fiber layer evaluation by optical coherence tomography in unaffected carriers with Leber's hereditary optic neuropathy mutations.	NO	Intervention	Cross-sectional study evaluating retinal nerve fiber layer in LHON. No treatment details reported.
680	Documenta Ophthalmologica. 108(3) (pp 231-240), 2004.	Kurtenbach A.	Inner retinal contributions to the multifocal electroretinogram: Patients with Leber hereditary optic neuropathy (LHON).	NO	Intervention	Examination of multifocal electroretinogram (mfERG) in LHON. Treatment details were not reported for included patients.

682	Chang Gung Medical Journal. 26(1) (pp 41-47), 2003.	Hung H.-L.	Clinical features of Leber's hereditary optic neuropathy with the 11778 mitochondrial DNA mutation in Taiwanese patients.	NO	Intervention	Description of clinical features in 11778 mitochondrial DNA mutation LHON Taiwanese patients. Treatment details not reported.
696	Japanese Journal of Ophthalmology. 46(6) (pp 660-667), 2002.	Mashima Y.	Macular nerve fibers temporal to fovea may have a greater potential to recover function in patients with Leber's hereditary optic neuropathy.	NO	Intervention	Treatment details or associated outcomes not reported.
701	Japanese Journal of Ophthalmology. 45(6) (pp 665-668), 2001.	Chuenkongkaew W.L.	Leber's hereditary optic neuropathy in Thailand.	NO	Intervention	Description of clinical features in LHON patients in Thailand. Treatment details/outcomes not reported.
710	American Journal of Ophthalmology. 130(6) (pp 803-812), 2000.	Kerrison J.B.	A case-control study of tobacco and alcohol consumption in leber hereditary optic neuropathy.	NO	Intervention	Examination of tobacco and alcohol consumption in LHON. Treatment details/outcomes were not reported.
712	Journal of Neuro-Ophthalmology. 19(2) (pp 89-99), 1999.	Yoshitomi T.	Comparison of threshold visual perimetry and objective pupil perimetry in clinical patients.	NO	Intervention	Comparison of threshold visual perimetry and objective pupil perimetry in untreated patients.
717	Graefe's Archive for Clinical and Experimental Ophthalmology. 237(3) (pp 207-211), 1999.	Ludtke H.	Pupillary light reflexes in patients with Leber's hereditary optic neuropathy.	NO	Intervention	Examination of pupillary behavior in LHON. No treatment details reported.
718	Investigative Ophthalmology and Visual Science. 40(11) (pp 2528-2534), 1999.	Bremner F.D.	Comparing pupil function with visual function in patients with Leber's hereditary optic neuropathy.	NO	Intervention	Examination of pupillary behavior and visual function in LHON. No treatment details reported.
720	American Journal of Ophthalmology. 126(2) (pp 291-295), 1998.	Jacobson D.M.	Relative afferent pupillary defects in patients with leber hereditary optic neuropathy and unilateral visual loss.	NO	Intervention	Examination of afferent pupillary defects in LHON. No treatment details reported.
726	Brain. 119(5) (pp 1481-1486), 1996.	Chalmers R.M.	A case-control study of Leber's hereditary optic neuropathy.	NO	Intervention	Treatment details or associated outcomes not reported.
729	Japanese Journal of Ophthalmology. 39(1) (pp 96-108), 1995.	Hotta Y.	Clinical features of Japanese Leber's hereditary optic neuropathy with 11778 mutation of mitochondrial DNA.	NO	Intervention	Presentation of clincal features of LHON in Japan. Treatments and associated outcomes not reported.
775	BMC Ophthalmology. 17(1):192, 2017 Oct 18.	Mashima Y	Visual prognosis better in eyes with less severe reduction of visual acuity one year after onset of Leber hereditary optic neuropathy caused by the 11,778 mutation.	NO	Intervention	Treatment details or associated outcomes not reported.
786	British Journal of Ophthalmology. 100(9):1232-7, 2016 09.	Balducci N	Macular nerve fibre and ganglion cell layer changes in acute Leber's hereditary optic neuropathy.	NO	Study design	Case series including four patients. Treatment not administered.

787	PLoS ONE [Electronic Resource]. 10(6):e0127906, 2015.	Carbonelli M	Macular Microcysts in Mitochondrial Optic Neuropathies: Prevalence and Retinal Layer Thickness Measurements.	NO	Intervention	Description of prevalence of macular microcysts in mitochondrial optic neuropathies. Treatment details not reported.
797	Investigative Ophthalmology & Visual Science. 55(10):6976-86, 2014 Sep 25.	Ogawa S	White matter consequences of retinal receptor and ganglion cell damage.	NO	Intervention	Cross-sectional study measuring cone-rod dystrophy in LHON. Treatment details not reported.
813	PLoS ONE [Electronic Resource]. 7(11):e50230, 2012.	Rizzo G	Secondary post-geniculate involvement in Leber's hereditary optic neuropathy.	NO	Intervention	Treatment details or associated outcomes not reported.
820	Journal of Neurology. 259(9):1801-7, 2012 Sep.	Milesi J	Patterns of white matter diffusivity abnormalities in Leber's hereditary optic neuropathy: a tract-based spatial statistics study.	NO	Intervention	Tract-based spatial statistics study not reporting treatment details.
827	Brain. 133(Pt 8):2426-38, 2010 Aug.	La Morgia C	Melanopsin retinal ganglion cells are resistant to neurodegeneration in mitochondrial optic neuropathies.	NO	Intervention	Treatment details or associated outcomes not reported.
834	Investigative Ophthalmology & Visual Science. 50(7):3112-5, 2009 Jul.	Kirkman MA	Quality of life in patients with leber hereditary optic neuropathy.	NO	Intervention	Treatment details or associated outcomes not reported.
835	Acta Opthalmologica. 86(6):630-3, 2008 Sep.	Yu-Wai-Man P	Investigation of auditory dysfunction in Leber hereditary optic neuropathy.	NO	Intervention	Examination of auditory dysfunction in LHON. Treatment details or associated outcomes not reported.
839	European Journal of Ophthalmology. 18(2):309-12, 2008 Mar-Apr.	Nemes A	Is there alteration in aortic stiffness in Leber hereditary optic neuropathy?.	NO	Intervention	Examination of aortic stiffness in LHON. Treatment details or associated outcomes not reported.
840	Eye. 22(9):1154-60, 2008 Sep.	Nagai-Kusuhara A	Evaluation of optic nerve head configuration in various types of optic neuropathy with Heidelberg Retina Tomograph.	NO	Intervention	Treatment details or associated outcomes not reported.
864	Graefes Archive for Clinical & Experimental Ophthalmology. 241(2):75-80, 2003 Feb.	Mashima Y	Optic disc excavation in the atrophic stage of Leber's hereditary optic neuropathy: comparison with normal tension glaucoma.	NO	Intervention	Treatment details or associated outcomes not reported.
880	British Journal of Ophthalmology. 84(5):534-5, 2000 May.	Nakamura M	Variable pattern of visual recovery of Leber's hereditary optic neuropathy.	NO	Intervention	Pattern of visual recovery in LHON outlined, however, treatment details or associated outcomes were not reported.
899	Archives of Ophthalmology. 111(4):495-8, 1993 Apr.	Johns DR	Leber's hereditary optic neuropathy. Clinical manifestations of the 14484 mutation.	NO	Intervention	Clinical manifestations of LHON presented. Treatment details or associated outcomes not reported.
908	Ophthalmic Paediatrics & Genetics. 5(1-2):125-30, 1985 Feb.	Nikoskelainen E	Fundus findings in Leber's hereditary optic neuroretinopathy.	NO	Intervention	Treatment details or associated outcomes not reported.
911	Archives of Ophthalmology.	Nikoskelainen E	Ophthalmoscopic findings in Leber's	NO	Intervention	Treatment details or associated outcomes not reported.

	100(10):1597-602, 1982 Oct.		hereditary optic neuropathy. I. Fundus findings in asymptomatic family members.			
913	Brain. 102(3):559-80, 1979 Sep.	Carroll WM	Leber's optic neuropathy: a clinical and visual evoked potential study of affected and asymptomatic members of a six generation family.	NO	Intervention	Case series where treatment details or associated outcomes not reported.
921	American Journal of Ophthalmology. 249 (pp 99-107), 2023.	Barboni P.	Childhood-Onset Leber Hereditary Optic Neuropathy-Clinical and Prognostic Insights	NO	Intervention	Treatment details or associated outcomes not reported.
951	British Journal of Ophthalmology. (no pagination), 2022. Article Number: 320580.	Siedlecki J.	Childhood versus early-teenage onset Leber's hereditary optic neuropathy: Visual prognosis and capacity for recovery	NO	Intervention	Treatment details or associated outcomes not reported.
968	Molecular Genetics and Metabolism. 136(3) (pp 219-225), 2022.	Hendrix C.L.F.	Screening and prevalence of cardiac abnormalities on electro- and echocardiography in a large cohort of patients with mitochondrial disease	NO	Intervention	Report of screening and prevalence of cardiac abnormalities on electro- and echocardiography in patients with mitochondrial disease. No details on treatment for LHON or associated outcomes reported.
1005	Neuro-Ophthalmology. Conference: 15th European Neuro-Ophthalmological Society, EUNOS 2022. Birmingham United Kingdom. 46(Supplement 1) (pp 94-95), 2022.	Battista M.	Childhood-onset Leber’s hereditary optic neuropathy - clinical and prognostic insights	NO	Intervention	No treatment details or outcomes of interest reported.
1019	Medicina (Kaunas, Lithuania). 58(9), 2022 Sep 07.	Liutkeviciene R	Relative Leukocyte Telomere Length and Telomerase Complex Regulatory Markers Association with Leber's Hereditary Optic Neuropathy	NO	Intervention	Evaluation of the association of relative leukocyte telomere length (RLTL) and telomerase complex regulatory markers with LHON. No treatment details reported.

Figure 4. Revised PRISMA for the RWE SLE

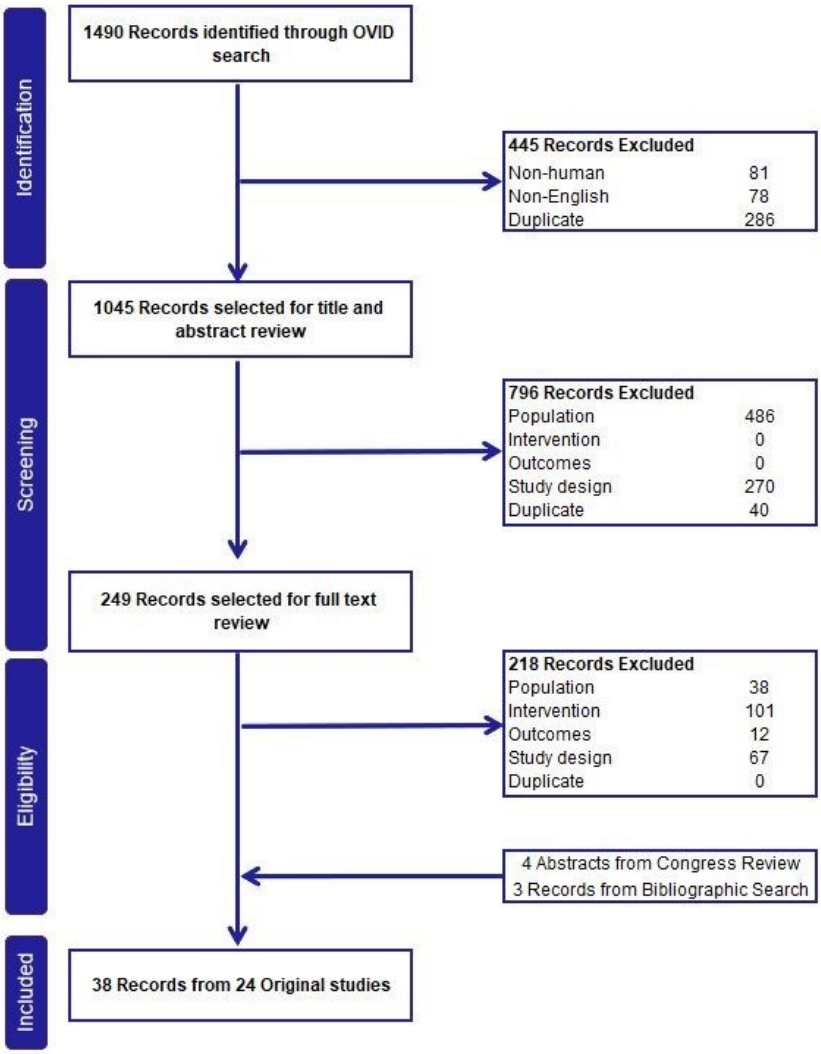


Table 32. Non-RCT quality assessment checklist

Study identifier (trial acronym)	CaRS1	CaRS2
Were selection/eligibility criteria adequately reported?	Yes	Yes
Was the selected population representative of that seen in normal practice?	Yes	Yes

Was an appropriate measure of variability reported?	Yes	No
Was loss to follow-up reported or explained?	No	No
Were at least 90% of those included at baseline followed up?	NR	NR
Were patients recruited prospectively?	No	No
Were patients recruited consecutively?	NR	NR
Did the study report relevant prognostic factors?	No	No

Chambers D RM, Woolacott N. Not only randomized controlled trials, but also case series should be considered in systematic reviews of rapidly developing technologies. J. Clin. Epidemiol. 2009;62(12):1253-1260.(80)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547]

Clarification questions

[November 2023]

File name	Version	Contains confidential information	Date
Delayed Responses_ID547 idebenone clarification letter PM for company_Responses_12Dec23_Redacted	1.0	Yes	12/12/2023

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Chiesi have been unable to provide responses to the following questions: A13, A22, A24, A25, A27d, A27e, and A29. Chiesi would like it noted that the company has only recently received all idebenone clinical data from Santhera as part of Santhera's divestment of idebenone to Chiesi. Therefore, given the additional questions shared and intensity of the requests from the EAG and the additional time required to analyse this new data, Chiesi have not been able to fulfil all requests within the short timeframe set. We did try to prioritise the priority questions but developing a response to A2 took considerable time and resource on its own.

Section A: Clarification on effectiveness data

Comparative Effectiveness Data

A2. Priority question. Given the concerns raised in question A1, the EAG considers the matching procedure used by the company in the LEROS trial to be flawed and at very high risk of bias.

Please use a propensity score matched or propensity score weighted analysis (or any other alternative method for the comparative analysis of IPD following the guidance of NICE DSU TSD17) analysis using:

a) The full LEROS – Intent-to-treat (ITT) population and full CaRS dataset;

b) The subset of idebenone treated patients from these populations ≤1 year after onset of symptoms.

In this analysis, please match individual patients rather than eyes, to mirror the structure of the economic model where patients rather than eyes are modelled. Please ensure all prognostic factors, including but not limited to: mtDNA mutation; time since symptom onset; age at symptom onset and baseline visual acuity (VA), are considered for matching.

Please compare the baseline characteristics of each matched cohort at baseline and report the following results:

- **Best recovery of logMAR visual acuity in either right or left eye;**
- **Change in best VA;**
- **CRR;**
- **Tables of transition probabilities between logMAR health states by visit.**

The natural history dataset analysed is characterised by its considerable heterogeneity, arising from several factors: the use of idebenone by some patients during certain visits,

follow-up visits were notably irregular, with some patients attending only baseline appointments and others having more frequent follow-ups; some visits included assessments of visual acuity (VA) for just one eye, rather than both; and the date of symptom onset was not always known. These factors collectively underscore the complex nature of the dataset and the need for meticulous analytical approaches to accurately interpret the results.

Table 1. Data collected in the CaRS studies

	CaRS-1	CaRS-2	Total
Original dataset			
All records (with or without VA assessment)	2986	2200	5186
Unique Visits	1499	1108	2607
Patients	373	219	592

Abbreviations: CaRS – Case Record Survey

All data was cleaned using the following criteria:

- Only idebenone naïve visits were considered,
- VA must had been assessed,
- month and year of the visit should be known,
- 1st symptoms onset occurred before or at the visit,
- both eyes had a VA assessment,
- the patient had at least 2 visits.

A final total of 4152 VA assessments, encompassing 2076 visits across 476 patients, was achieved.

All visit dates for each patient were combined to create a set with 6376 visit pairs. A time delta, representing the duration between each pair of visits, was then calculated and associated with these pairs. Time between visits could vary from 1 day to 514.1 months, being mean time of 34.4 months. This information was subsequently used to select patients for the analysis.

Table 2. Data which is evaluable for analysis

	CaRS-1	CaRS-2	Total
Evaluable for Analysis			
Unique Visits	1079	997	2076
Patients	265	211	476
VA assessments	2158	1994	4152
Pairs of visits	3049	3327	6376
Months between visit			
Mean ± SD	37.6±63.4	31.4±39.7	34.4±52.5
Median (Q1-Q3)	10.1 (2.6 - 43.5)	12.6 (3.2 - 47.6)	11.7 (2.9 - 45.8)
Min - Max	0.0 - 514.1	0.0 - 196.4	0.0 - 514.1

Abbreviations: CaRS – Case Record Survey; Q – Quartile; SD – Standard deviation

Propensity Scores (PS) were derived from a logistic regression model, incorporating variables such as gender, mutation, age at first symptom onset at baseline, time since the most recent symptom onset at baseline, time since first symptom onset at baseline, number of symptomatic eyes at baseline, and baseline VA logMAR for each eye. NH VA values were imputed for enhanced consistency and accuracy. Specifically, any converted VA measurement with a logMAR value greater than 1.68 was adjusted to 1.8, as well any other value off-chart. This imputation was necessitated by the high prevalence of patients measured using the Snellen and decimal systems. Additionally, there was uncertainty regarding the uniformity of off-chart measurements, such as counting fingers and hand motion, particularly in terms of the distance used for these assessments. This step ensured standardization across different measurement methods. A Propensity Score Matching (PSM) was executed using the nearest neighbor method with a caliper set to 0.2 times the standard deviation of the logit of the PS. All calculations were performed in SAS 9.4, utilising 'proc psmatch' for the PSM.

For the selection of patients and visits, a specific approach was employed at each time point. Taking 24 months as an example, all NH patients with pairs of visits showing a 24-month delta within a 3-month window were selected. Subsequently, for each NH patient,

the visit pair that most closely matched the mean time since the first symptoms onset, as observed in LEROS patients, was identified and chosen. This methodology aimed to align the NH patient data as closely as possible with the LEROS mean. The final dataset, comprising only one visit per patient, was then utilized for PSM.

For the subacute analysis, a second layer of filtering was applied to the NH visit selection process. In the initial phase, only those visits where the most recent symptom onset occurred within the last year were considered. This meant that for inclusion in the pooled visits dataset, the time since the most recent symptom onset had to be less than one year.

PSM LEROS ITT patients at 24 months visit

A total of 125 LEROS Intent-to-Treat (ITT) patients were followed up for 24 months. At baseline, the mean duration since the onset of their first symptoms was 18.2 months.

In the NH cohort, there were a total of 270 possible pairs of visits identified among 84 patients.

Table 3. Patients to be matched

Description	CaRS-1	CaRS-2	Total
Possible pairs of visits	128	142	270
Patients	47	37	84

Abbreviations: CaRS – Case Record Survey

After applying the matching criteria, a total of 68 patients from the LEROS ITT group were successfully matched with 68 patients from the NH cohort.

Table 4. Patients that have been matched

Description	CaRS-1	CaRS-2	LEROS
Matched Patients	36	32	68

Abbreviations: CaRS – Case Record Survey

Matching diagnostic

In Figure 1, please interpret the variable names as follows:

- DM_GENDERC: Gender
- DM_AGE_ONSET: Age at first symptom onset at baseline
- VST_MR_ONSETM: Months since the most recent symptom onset at baseline
- VST_1ST_ONSETM: Months since the first symptom onset at baseline
- EYES_BL: Number of symptomatic eyes at baseline
- VST_VAI_left: Baseline visual acuity (VA) logMAR for the left eye
- VST_VAI_right: Baseline VA logMAR for the right eye.

It is not possible to show in this graphic the differences of the variable mutation since is non-binary.

Figure 1. Standardised mean differences between treated and controlled observations

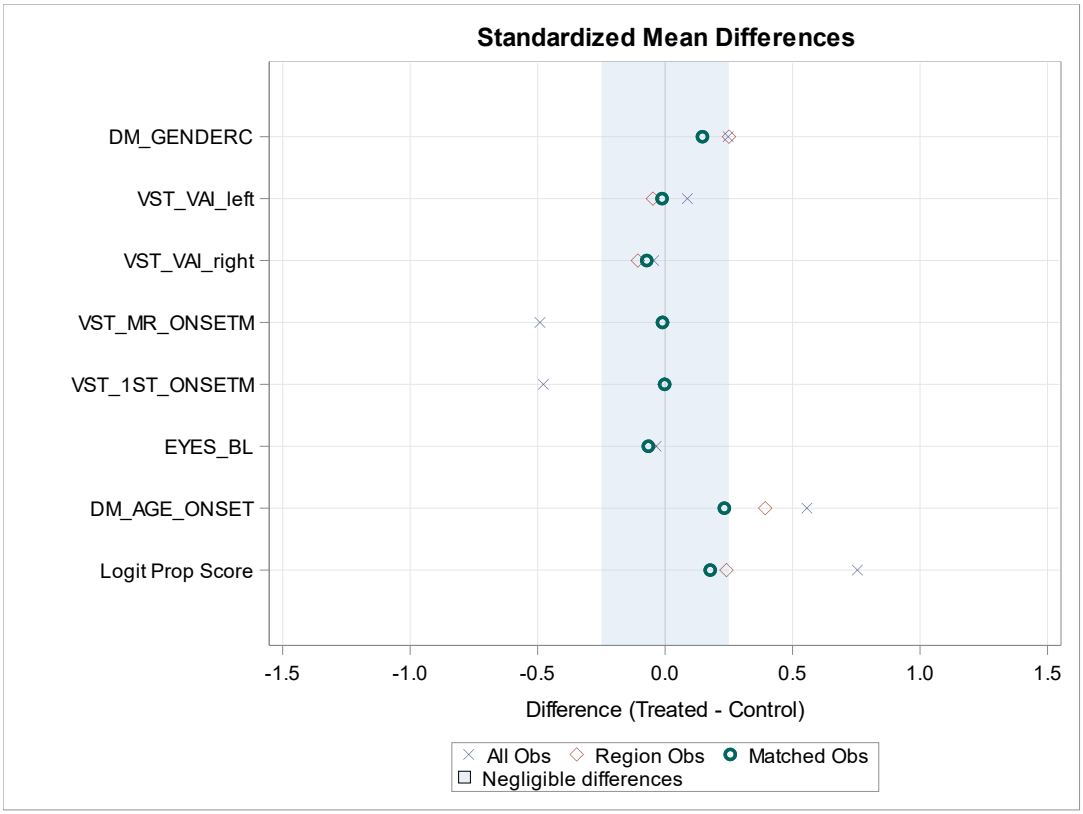


Table 5. Comparison of baseline characteristics in matched analysis

Baseline Characteristics	NH	Raxone	Total
Gender			
Female	11 (16.2%)	15 (22.1%)	26 (19.1%)
Male	57 (83.8%)	53 (77.9%)	110 (80.9%)
Total	68	68	136
Mutations			
G11778A	40 (58.8%)	39 (57.4%)	79 (58.1%)
G3460A	14 (20.6%)	15 (22.1%)	29 (21.3%)
Other	5 (7.4%)	1 (1.5%)	6 (4.4%)
T14484C	9 (13.2%)	13 (19.1%)	22 (16.2%)
Total	68	68	136
Age at 1st symptom onset			
N	68	68	136
Mean ± SD	26.2±15.3	29.7±13.6	27.9±14.5
Median (Q1-Q3)	21.0 (15.5 - 36.5)	26.7 (19.1 - 39.1)	23.1 (16.8 - 38.2)
Min - Max	6.0 - 63.0	8.8 - 64.2	6.0 - 64.2
Eyes affected at baseline			
1	0 (0.0%)	4 (5.9%)	4 (2.9%)
2	68 (100.0%)	64 (94.1%)	132 (97.1%)
Total	68	68	136
Months since 1st symptoms onset at baseline			
N	68	68	136
Mean ± SD	18.2±22.3	18.1±16.6	18.2±19.6
Median (Q1-Q3)	13.2 (5.5 - 21.4)	11.8 (6.1 - 23.8)	12.3 (6.1 - 22.1)

Min - Max	0.0 - 134.1	0.3 - 58.3	0.0 - 134.1
Months since most recent symptoms onset at baseline			
N	68	68	136
Mean ± SD	17.1±21.9	16.3±16.5	16.7±19.3
Median (Q1-Q3)	11.3 (4.1 - 20.4)	9.4 (4.6 - 23.5)	10.3 (4.2 - 21.8)
Min - Max	0.0 - 134.1	0.0 - 57.6	0.0 - 134.1
Baseline VA logMAR			
N	136	136	272
Mean ± SD	1.30±0.51	1.28±0.54	1.29±0.52
Median (Q1-Q3)	1.34 (1.00 - 1.80)	1.45 (0.95 - 1.80)	1.40 (1.00 - 1.80)
Min - Max	-0.20 - 1.80	-0.12 - 1.80	-0.20 - 1.80
Baseline VA			
Light Perception	0 (0.00%)	2 (1.47%)	2 (0.74%)
Hand Motion	9 (6.77%)	16 (11.76%)	25 (9.29%)
Counting Fingers	34 (25.56%)	19 (13.97%)	53 (19.70%)
logMAR >= 1.3 and < 1.7	41 (30.83%)	46 (33.82%)	87 (32.34%)
logMAR >= 1.0 and < 1.3	22 (16.54%)	18 (13.24%)	40 (14.87%)
logMAR >= 0.6 and < 1.0	15 (11.28%)	16 (11.76%)	31 (11.52%)
logMAR >= 0.3 and < 0.6	6 (4.51%)	7 (5.15%)	13 (4.83%)
logMAR < 0.3	6 (4.51%)	12 (8.82%)	18 (6.69%)
Total	133	136	269
Baseline best VA logMAR			
N	68	68	136
Mean ± SD	1.19±0.53	1.16±0.60	1.18±0.56

Median (Q1-Q3)	1.30 (0.90 - 1.80)	1.31 (0.69 - 1.65)	1.30 (0.75 - 1.73)
Min - Max	-0.20 - 1.80	-0.12 - 1.80	-0.20 - 1.80
Baseline best VA			
Light Perception	0 (0.00%)	1 (1.47%)	1 (0.74%)
Hand Motion	4 (5.88%)	6 (8.82%)	10 (7.35%)
Counting Fingers	13 (19.12%)	9 (13.24%)	22 (16.18%)
logMAR >= 1.3 and < 1.7	20 (29.41%)	20 (29.41%)	40 (29.41%)
logMAR >= 1.0 and < 1.3	13 (19.12%)	9 (13.24%)	22 (16.18%)
logMAR >= 0.6 and < 1.0	10 (14.71%)	9 (13.24%)	19 (13.97%)
logMAR >= 0.3 and < 0.6	4 (5.88%)	4 (5.88%)	8 (5.88%)
logMAR < 0.3	4 (5.88%)	10 (14.71%)	14 (10.29%)
Total	68	68	136

Abbreviations: NH – Natural history; Q – Quartile; SD – Standard deviation; VA – Visual acuity

Best recovery of VA logMAR and change in Best VA were evaluated using analysis of covariance (ANCOVA) and CRR was evaluated using logistic regression. Two distinct modelling approaches were employed. In the first model, only the treatment was considered as a covariate. For the second model, it was expanded the scope to include both the mutation type and the interaction between the treatment and mutation. However, this extended model was specifically applied to the dataset containing only the three major mutations. The decision to exclude the 'other' mutations category was driven by the very small number of patients within this group, which could potentially introduce bias into the model.

Table 6. Best recovery of VA

Best recovery of VA logMAR			
Treatment	**LS-Means(SE)**	**LS-Means 95% CI**	**LS-Means p-value**
Raxone	-0.28 (0.07)	[-0.42; -0.15]	<.0001

Best recovery of VA logMAR			
Treatment	**LS-Means(SE)**	**LS-Means 95% CI**	**LS-Means p-value**
NH	-0.24 (0.07)	[-0.37; -0.10]	0.0008
Difference	-0.05 (0.10)	[-0.24; 0.15]	0.6280
ANCOVA with treatment as covariate			

Abbreviations: CI – Confidence interval; LS – Least squares; NH – Natural history; SE – Standard error; VA – Visual acuity

Table 7. Best recovery of VA split by mutation type

Best recovery of VA logMAR				
Treatment	**Major 3 mutations**	**LS-Means(SE)**	**LS-Means 95% CI**	**LS-Means p-value**
Raxone	_	-0.31 (0.07)	[-0.45; -0.17]	<.0001
NH	_	-0.36 (0.08)	[-0.52; -0.20]	<.0001
Raxone	G11778A	-0.21 (0.08)	[-0.38; -0.04]	0.0153
Raxone	G3460A	-0.08 (0.14)	[-0.35; 0.19]	0.5523
Raxone	T14484C	-0.64 (0.15)	[-0.93; -0.35]	<.0001
NH	G11778A	-0.07 (0.08)	[-0.24; 0.10]	0.4036
NH	G3460A	-0.47 (0.14)	[-0.75; -0.19]	0.0012
NH	T14484C	-0.54 (0.18)	[-0.89; -0.19]	0.0026
Difference	_	0.05 (0.11)	[-0.16; 0.26]	0.6458
Difference	G11778A	-0.14 (0.12)	[-0.37; 0.10]	0.2476
Difference	G3460A	0.39 (0.20)	[0.00; 0.78]	0.0508
Difference	T14484C	-0.10 (0.23)	[-0.55; 0.35]	0.6642

ANCOVA with treatment and mutation as covariates

Type 3 Test of Fixed Effects	**p-value**
Treatment	0.6458
Major 3 Mutation	0.0027
Interaction Treatment * Major 3 Mutation	0.0709

Abbreviations: CI – Confidence interval; LS – Least squares; NH – Natural history; SE – Standard Error; VA – Visual acuity

Table 8. Change in best VA

Change in Best VA logMAR			
Treatment	**LS-Means(SE)**	**LS-Means 95% CI**	**LS-Means p-value**
Raxone	-0.13 (0.08)	[-0.27; 0.02]	0.0972
NH	-0.11 (0.08)	[-0.26; 0.04]	0.1523
Difference	-0.02 (0.11)	[-0.23; 0.19]	0.8708
ANCOVA with treatment as covariate			

Abbreviations: CI – Confidence interval; LS – Least squares; NH – Natural history; SE – Standard Error; VA – Visual acuity

Table 9. Change in best VA split by mutation type

Change in Best VA logMAR				
Treatment	**Major 3 mutations**	**LS-Means(SE)**	**LS-Means 95% CI**	**LS-Means p-value**
Raxone	_	-0.14 (0.08)	[-0.29; 0.02]	0.0850
NH	_	-0.24 (0.09)	[-0.41; -0.07]	0.0068
Raxone	G11778A	-0.07 (0.09)	[-0.25; 0.11]	0.4359
Raxone	G3460A	0.17 (0.15)	[-0.13; 0.46]	0.2626
Raxone	T14484C	-0.50 (0.16)	[-0.82; -0.19]	0.0019
NH	G11778A	0.07 (0.09)	[-0.11; 0.25]	0.4708
NH	G3460A	-0.30 (0.15)	[-0.61; 0.00]	0.0491
NH	T14484C	-0.48 (0.19)	[-0.86; -0.10]	0.0133
Difference	_	0.10 (0.12)	[-0.13; 0.34]	0.3807
Difference	G11778A	-0.14 (0.13)	[-0.39; 0.12]	0.2892
Difference	G3460A	0.47 (0.21)	[0.05; 0.89]	0.0289
Difference	T14484C	-0.02 (0.25)	[-0.52; 0.47]	0.9228

Change in Best VA logMAR				
Treatment	**Major 3 mutations**	**LS-Means(SE)**	**LS-Means 95% CI**	**LS-Means p-value**
ANCOVA with treatment and mutation as covariates				

Type 3 Test of Fixed Effects	**p-value**
Treatment	0.3807
Major 3 Mutation	0.0028
Interaction Treatment * Major 3 Mutation	0.0534

Abbreviations: CI – Confidence interval; LS – Least squares; NH – Natural history; SE – Standard Error; VA – Visual acuity

Table 10. CRR split for overall cohort and mutation type

CRR	NH	Raxone	Odds Ratio [95% CI] p-value
CRR	26 (38.2%)	30 (44.1%)	1.28 [0.64; 2.54] 0.4857
CRR in G11778A	10 (25.0%)	13 (33.3%)	1.50 [0.57; 4.07] 0.4145
CRR in G3460A	10 (71.4%)	4 (26.7%)	0.15 [0.03; 0.69] 0.0142
CRR in T14484C	4 (44.4%)	12 (92.3%)	15.00 [1.75; 338.7] 0.0116
CRR in other mutations	2 (40.0%)	1 (100.0%)	-

Type 3 Test of Fixed Effects	**p-value**
Treatment	0.0287
Major 3 Mutation	0.0137
Interaction Treatment * Major 3 Mutation	0.0046

Abbreviations: CI – Confidence interval; CRR – Complete recovery of response; NH – Natural history

Table 11. Transition probabilities between logMAR health states by visit

Baseline best VA	Visit Best VA						
	Hand Motion	Counting Fingers	logMAR >= 1.3 and < 1.7	logMAR >= 1.0 and < 1.3	logMAR >= 0.6 and < 1.0	logMAR >= 0.3 and < 0.6	logMAR < 0.3
	N	N	N	N	N	N	N
Light Perception	.	.	1	.	.	.	.
Hand Motion	5	3	1	.	.	.	1
Counting Fingers	1	8	8	.	2	1	2
logMAR >= 1.3 and < 1.7	.	4	26	4	1	2	3
logMAR >= 1.0 and < 1.3	1	1	5	4	5	1	5
logMAR >= 0.6 and < 1.0	.	1	1	4	6	2	5
logMAR >= 0.3 and < 0.6	.	1	.	.	.	4	3
logMAR < 0.3	2	.	3	.	.	2	7

Abbreviations: VA – Visual acuity

PSM LEROS subacute patients at 24 months visit

A total of 70 LEROS subacute patients were followed up for 24 months. At baseline, the mean duration since the onset of their first symptoms was 8.0 months.

In the NH cohort, there were a total of 152 possible pairs of visits identified among 53 patients.

Table 12. Patients to be matched (subacute)

Description	CaRS-1	CaRS-2	Total
Possible pairs of visits	69	83	152
Patients	26	27	53

Abbreviations: CaRS – Case Record Survey

After applying the matching criteria, a total of 44 patients from the LEROS subacute group were successfully matched with 44 patients from the NH cohort.

Table 13. Patients that have been matched (subacute)

Description	CaRS-1	CaRS-2	LEROS
Matched Patients	19	25	44

Abbreviations: CaRS – Case Record Survey

Matching diagnostic

In Figure 2, please interpret the variable names as follows:

- DM_GENDERC: Gender
- DM_AGE_ONSET: Age at first symptom onset at baseline
- VST_MR_ONSETM: Months since the most recent symptom onset at baseline
- VST_1ST_ONSETM: Months since the first symptom onset at baseline
- EYES_BL: Number of symptomatic eyes at baseline
- VST_VAI_left: Baseline visual acuity (VA) logMAR for the left eye
- VST_VAI_right: Baseline VA logMAR for the right eye.

It is not possible to show in this graphic the differences of the variable mutation since is non-binary.

Figure 2. Standardised mean differences between treated and controlled observations (subacute)

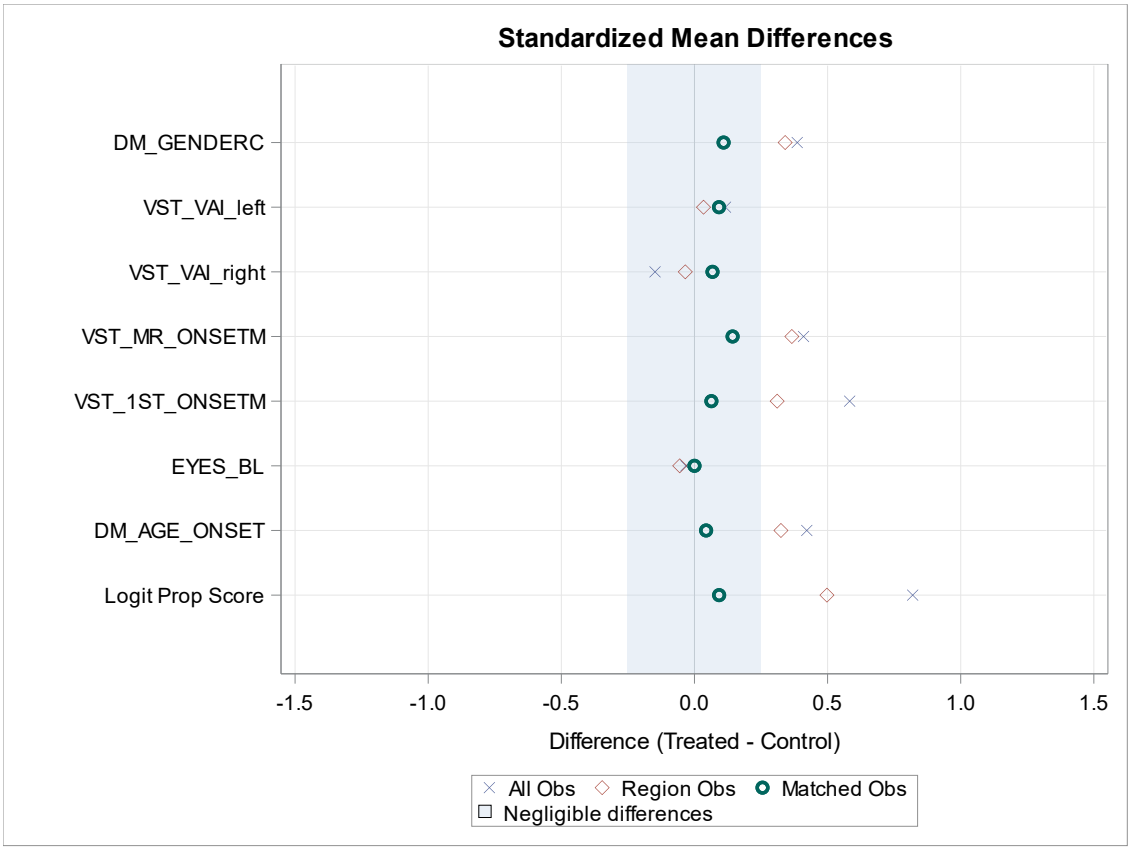


Table 14. Comparison of baseline characteristics in matched analysis (subacute)

Baseline Characteristics	NH	Raxone	Total
Gender			
Female	8 (18.2%)	10 (22.7%)	18 (20.5%)
Male	36 (81.8%)	34 (77.3%)	70 (79.5%)
Total	44	44	88
Grouped mutations			
G11778A	27 (61.4%)	19 (43.2%)	46 (52.3%)
G3460A	10 (22.7%)	11 (25.0%)	21 (23.9%)
Other	3 (6.8%)	1 (2.3%)	4 (4.5%)
T14484C	4 (9.1%)	13 (29.5%)	17 (19.3%)

Total	44	44	88
Age at 1st symptom onset			
N	44	44	88
Mean ± SD	27.8±17.2	28.4±12.6	28.1±15.0
Median (Q1-Q3)	22.0 (14.0 - 40.0)	27.5 (19.1 - 36.3)	24.5 (16.0 - 38.5)
Min - Max	6.0 - 63.0	12.1 - 62.3	6.0 - 63.0
Eyes affected at baseline			
1	0 (0.0%)	4 (9.1%)	4 (4.5%)
2	44 (100.0%)	40 (90.9%)	84 (95.5%)
Total	44	44	88
Months since 1st symptoms onset at baseline			
N	44	44	88
Mean ± SD	5.9±3.1	6.2±3.7	6.0±3.4
Median (Q1-Q3)	6.2 (4.0 - 8.1)	6.0 (3.3 - 8.6)	6.1 (3.7 - 8.2)
Min - Max	0.0 - 12.6	0.3 - 16.3	0.0 - 16.3
Months since most recent symptoms onset at baseline			
N	44	44	88
Mean ± SD	4.7±3.1	5.1±3.1	4.9±3.1
Median (Q1-Q3)	4.7 (1.8 - 7.4)	4.6 (2.6 - 7.5)	4.7 (2.2 - 7.5)
Min - Max	0.0 - 10.2	0.3 - 11.6	0.0 - 11.6
Baseline VA logMAR			
N	88	88	176
Mean ± SD	1.24±0.54	1.28±0.47	1.26±0.51
Median (Q1-Q3)	1.30 (1.00 - 1.80)	1.34 (1.08 - 1.66)	1.33 (1.00 - 1.74)

Min - Max	-0.20 - 1.80	-0.04 - 1.80	-0.20 - 1.80
Baseline VA			
Hand Motion	0 (0.00%)	6 (6.82%)	6 (3.41%)
Counting Fingers	24 (27.27%)	11 (12.50%)	35 (19.89%)
logMAR >= 1.3 and < 1.7	29 (32.95%)	37 (42.05%)	66 (37.50%)
logMAR >= 1.0 and < 1.3	14 (15.91%)	15 (17.05%)	29 (16.48%)
logMAR >= 0.6 and < 1.0	9 (10.23%)	10 (11.36%)	19 (10.80%)
logMAR >= 0.3 and < 0.6	4 (4.55%)	3 (3.41%)	7 (3.98%)
logMAR < 0.3	8 (9.09%)	6 (6.82%)	14 (7.95%)
Total	88	88	176
Baseline best VA logMAR			
N	44	44	88
Mean ± SD	1.09±0.58	1.15±0.53	1.12±0.56
Median (Q1-Q3)	1.26 (0.70 - 1.50)	1.29 (0.94 - 1.53)	1.29 (0.70 - 1.51)
Min - Max	-0.20 - 1.80	-0.04 - 1.80	-0.20 - 1.80
Baseline best VA			
Hand Motion	0 (0.00%)	2 (4.55%)	2 (2.27%)
Counting Fingers	8 (18.18%)	4 (9.09%)	12 (13.64%)
logMAR >= 1.3 and < 1.7	14 (31.82%)	16 (36.36%)	30 (34.09%)
logMAR >= 1.0 and < 1.3	8 (18.18%)	9 (20.45%)	17 (19.32%)
logMAR >= 0.6 and < 1.0	5 (11.36%)	6 (13.64%)	11 (12.50%)
logMAR >= 0.3 and < 0.6	2 (4.55%)	1 (2.27%)	3 (3.41%)
logMAR < 0.3	7 (15.91%)	6 (13.64%)	13 (14.77%)
Total	44	44	88

Abbreviations: NH – Natural history; Q – Quartile; SD – Standard deviation; VA – Visual acuity

Best recovery of VA logMAR and change in Best VA were evaluated using analysis of covariance (ANCOVA) and CRR was evaluated using logistic regression. Two distinct modelling approaches were employed. In the first model, only the treatment was considered as a covariate. For the second model, it was expanded the scope to include both the mutation type and the interaction between the treatment and mutation. However, this extended model was specifically applied to the dataset containing only the three major mutations. The decision to exclude the 'other' mutations category was driven by the very small number of patients within this group, which could potentially introduce bias into the model.

Table 15. Best recovery of VA (subacute)

Best recovery of VA logMAR			
Treatment	**LS-Means(SE)**	**LS-Means 95% CI**	**LS-Means p-value**
Raxone	-0.31 (0.10)	[-0.50; -0.12]	0.0020
NH	-0.27 (0.10)	[-0.46; -0.08]	0.0064
Difference	-0.04 (0.14)	[-0.31; 0.23]	0.7829
ANCOVA with treatment as covariate			

Abbreviations: CI – Confidence interval; LS – Least squares; NH – Natural history; SE – Standard error; VA – Visual acuity

Table 16. Best recovery of VA split by mutation type (subacute)

Best recovery of VA logMAR				
Treatment	**Major 3 mutations**	**LS-Means(SE)**	**LS-Means 95% CI**	**LS-Means p-value**
Raxone	_	-0.26 (0.09)	[-0.44; -0.08]	0.0058
NH	_	-0.52 (0.12)	[-0.76; -0.29]	<.0001
Raxone	G11778A	-0.27 (0.13)	[-0.53; 0.00]	0.0464
Raxone	G3460A	0.11 (0.17)	[-0.23; 0.46]	0.5181
Raxone	T14484C	-0.61 (0.16)	[-0.93; -0.29]	0.0003
NH	G11778A	-0.07 (0.11)	[-0.29; 0.15]	0.5481

NH	G3460A	-0.58 (0.18)	[-0.95; -0.22]	0.0020
NH	T14484C	-0.92 (0.29)	[-1.50; -0.35]	0.0020
Difference	_	0.27 (0.15)	[-0.03; 0.57]	0.0765
Difference	G11778A	-0.20 (0.17)	[-0.54; 0.14]	0.2484
Difference	G3460A	0.70 (0.25)	[0.20; 1.20]	0.0071
Difference	T14484C	0.31 (0.33)	[-0.35; 0.97]	0.3490

ANCOVA with treatment and mutation as covariates

Type 3 Test of Fixed Effects	**p-value**
Treatment	0.0765
Major 3 Mutation	0.0069
Interaction Treatment * Major 3 Mutation	0.0139

Abbreviations: CI – Confidence interval; LS – Least squares; NH – Natural history; SE – Standard error; VA – Visual acuity

Table 17. Change in best VA (subacute)

Change in Best VA logMAR			
Treatment	**LS-Means(SE)**	**LS-Means 95% CI**	**LS-Means p-value**
Raxone	-0.12 (0.12)	[-0.37; 0.12]	0.3224
NH	-0.02 (0.12)	[-0.27; 0.23]	0.8756
Difference	-0.10 (0.18)	[-0.45; 0.24]	0.5549
ANCOVA with treatment as covariate			

Abbreviations: CI – Confidence interval; LS – Least squares; NH – Natural history; SE – Standard error; VA – Visual acuity

Table 18. Change in best VA split by mutation type (subacute)

Change in Best VA logMAR				
Treatment	**Major 3 mutations**	**LS-Means(SE)**	**LS-Means 95% CI**	**LS-Means p-value**
Raxone	_	-0.05 (0.12)	[-0.28; 0.18]	0.6399
NH	_	-0.30 (0.15)	[-0.60; 0.01]	0.0571
Raxone	G11778A	-0.12 (0.17)	[-0.46; 0.22]	0.4887
Raxone	G3460A	0.47 (0.22)	[0.02; 0.91]	0.0392
Raxone	T14484C	-0.51 (0.20)	[-0.92; -0.10]	0.0145
NH	G11778A	0.18 (0.14)	[-0.11; 0.46]	0.2204
NH	G3460A	-0.47 (0.23)	[-0.93; 0.00]	0.0497
NH	T14484C	-0.60 (0.37)	[-1.33; 0.14]	0.1097
Difference	_	0.24 (0.19)	[-0.14; 0.62]	0.2119
Difference	G11778A	-0.29 (0.22)	[-0.73; 0.15]	0.1884
Difference	G3460A	0.93 (0.32)	[0.29; 1.58]	0.0050
Difference	T14484C	0.09 (0.42)	[-0.76; 0.93]	0.8406

ANCOVA with treatment and mutation as covariates

Type 3 Test of Fixed Effects	**p-value**
Treatment	0.2119
Major 3 Mutation	0.0492
Interaction Treatment * Major 3 Mutation	0.0098

Abbreviations: CI – Confidence interval; LS – Least squares; NH – Natural history; SE – Standard error; VA – Visual acuity

Table 19. CRR split for overall cohort and mutation type (subacute)

CRR	NH	Raxone	Odds Ratio [95% CI] p-value
CRR	19 (43.2%)	24 (54.5%)	1.58 [0.68; 3.70] 0.2858

CRR in G11778A	7 (25.9%)	9 (47.4%)	2.57 [0.75; 9.28] 0.1336
CRR in G3460A	8 (80.0%)	4 (36.4%)	0.14 [0.02; 0.91] 0.0392
CRR in T14484C	3 (75.0%)	10 (76.9%)	1.11 [0.05; 13.43] 0.9371
CRR in other mutations	1 (33.3%)	1 (100.0%)	-

Type 3 Test of Fixed Effects	**p-value**
Treatment	0.9368
Major 3 Mutation	0.0115
Interaction Treatment * Major 3 Mutation	0.0530

Abbreviations: CI – Confidence interval; CRR – Complete recovery of response; NH – Natural history

Table 20. Transition probabilities between logMAR health states by visit (subacute)

Baseline best VA	**Visit Best VA**							
	Light Perception	**Hand Motion**	**Counting Fingers**	**logMAR >= 1.3 and < 1.7**	**logMAR >= 1.0 and < 1.3**	**logMAR >= 0.6 and < 1.0**	**logMAR >= 0.3 and < 0.6**	**logMAR < 0.3**
	N	**N**	**N**	**N**	**N**	**N**	**N**	**N**
Hand Motion	.	.	.	1	.	.	.	1
Counting Fingers	1	2	4	3	.	.	.	2
logMAR >= 1.3 and < 1.7	.	.	3	15	2	3	3	4
logMAR >= 1.0 and < 1.3	.	.	2	5	3	2	1	4

logMAR >= 0.6 and < 1.0	.	.	1	1	2	4	1	2
logMAR >= 0.3 and < 0.6	.	.	1	.	.	.	.	2
logMAR < 0.3	.	1	3	4	1	.	1	3

Abbreviations: VA – Visual acuity

Natural history

A3. Using the full data set from CaRS I and CaRS II and the placebo arm of RHODOS please provide an estimate of spontaneous recovery for LHON patients. Please provide appropriate regression analyses investigating the relationship between spontaneous recovery and: i) mutation status, ii) age at symptom onset, iii) time since symptom onset, iv) VA at nadir.

In the current analysis, the base dataset utilised is identical to the initial detailed in the previous response, which underwent thorough cleaning based on specific criteria, such as considering only idebenone-naïve visits, ensuring VA assessments were conducted, and having known visit dates, among others. This process resulted in a final dataset encompassing 4152 VA assessments across 2076 visits and 476 patients.

Outcomes across all visits in an observation time-unrestricted analysis

Table 21. Baseline characteristics in CaRS studies

Baseline Characteristics	CaRS-1	CaRS-2	Total
Grouped mutations (char)			
G11778A	177 (66.8%)	150 (71.1%)	327 (68.7%)
G3460A	44 (16.6%)	30 (14.2%)	74 (15.5%)
Other	13 (4.9%)	0 (0.0%)	13 (2.7%)
T14484C	31 (11.7%)	31 (14.7%)	62 (13.0%)
Total	265	211	476
Age at 1st symptom onset			
N	264	211	475
Mean ± SD	27.6±14.7	29.8±15.1	28.6±14.9
Median (Q1-Q3)	24.0 (17.0 - 36.0)	25.0 (18.0 - 41.0)	24.0 (17.0 - 38.0)
Min - Max	6.0 - 78.0	6.0 - 68.0	6.0 - 78.0
Months since first symptoms onset at Baseline			

N	265	211	476
Mean ± SD	64.1±132.8	3.2±5.6	37.1±103.6
Median (Q1-Q3)	4.8 (0.9 - 33.0)	1.5 (0.5 - 3.5)	2.5 (0.7 - 7.7)
Min - Max	0.0 - 629.0	0.0 - 47.7	0.0 - 629.0
Months since most recent symptom's onset at Baseline			
N	265	211	476
Mean ± SD	59.8±127.7	2.7±5.4	34.5±99.4
Median (Q1-Q3)	3.2 (0.7 - 20.3)	0.9 (0.3 - 2.8)	1.7 (0.4 - 6.8)
Min - Max	0.0 - 595.0	0.0 - 47.7	0.0 - 595.0
Months since baseline at last visit			
N	265	211	476
Mean ± SD	43.9±80.1	27.7±44.4	36.7±67.1
Median (Q1-Q3)	8.4 (0.0 - 44.4)	6.5 (1.8 - 31.3)	7.5 (1.1 - 38.5)
Min - Max	0.0 - 514.1	0.0 - 196.4	0.0 - 514.1

Abbreviations: NH – Natural history; Q – Quartile; SD – Standard deviation; VA – Visual acuity

Table 22. Eyes with CRR in CaRS studies and split by mutation

Eyes with CRR	CaRS-1	CaRS-2	Total
CRR			
No	468 (88.3%)	355 (84.1%)	823 (86.4%)
Yes	62 (11.7%)	67 (15.9%)	129 (13.6%)
Total	530	422	952
G11778A	28 (7.9%)	38 (12.7%)	66 (10.1%)
G3460A	22 (25.0%)	14 (23.3%)	36 (24.3%)
T14484C	9 (14.5%)	15 (24.2%)	24 (19.4%)
Other	3 (11.5%)	-	3 (11.5%)

Abbreviations: CaRS – Case Record Survey; CRR – Complete recovery of response

Table 23. Output from regression analysis (eyes)

Effect	Odds Ratio [95% CI]	p-value
G3460A vs G11778A	2.86 [1.81; 4.49]	0.0000
T14484C vs G11778A	2.14 [1.26; 3.53]	0.0055
Age at first symptoms onset	0.97 [0.96; 0.99]	0.0002
Months since first symptoms on	1.00 [0.99; 1.00]	0.0069
Months since most recent symptom onset	1.00 [0.99; 1.00]	0.0121
Nadir	1.21 [0.84; 1.78]	0.3117

Type 3 Test of Fixed Effects	p-value
Major 3 Mutations	<.0001

Abbreviations: CI – Confidence interval

A logistic regression model was applied to each subgroup in analysis. The mutation-specific analysis was limited to the major three mutations, as only a few subjects possessed other mutations. Including these mutations in the model could have introduced bias, hence their exclusion to ensure a more accurate and representative analysis.

The analysis of odds ratios in the study reveals significant differences in the likelihood of the outcome based on genetic mutations and age at the onset of symptoms. The odds of the outcome for the G3460A mutation are approximately 186% higher than for the G11778A mutation, as indicated by an odds ratio of 2.86 and a highly significant p-value of 0.0000. Similarly, the T14484C mutation shows about 114% higher odds compared to the G11778A mutation, with an odds ratio of 2.14 and a significant p-value of 0.0055. These findings underscore the pivotal role that specific genetic mutations play in the outcome being studied, suggesting a substantial genetic influence.

In contrast, age at the first symptom onset demonstrates a slightly protective effect, with a decrease in the odds of the outcome as age increases, shown by an odds ratio of 0.97. This is a statistically significant result, supported by a p-value of 0.0002, indicating a potentially important age-related factor in the outcome. The effect of time since the first and most recent symptoms onset has less impact. Both variables show

an odds ratio of 1.00, with statistically significant but small effect sizes, as reflected in the p-values of 0.0069 and 0.0121, respectively.

In contrast, the analysis of the nadir with an odds ratio of 1.21 does not reach statistical significance, as indicated by a p-value of 0.3117. This lack of significance implies that nadir may not be a strong predictor of the outcome in this context. Overall, the results highlight the significant impact of genetic mutations and age at symptom onset on the outcome, while suggesting a more limited role for the timing of symptom onset and nadir in influencing the outcome.

Table 24. Patients with CRR in CaRS studies and split by mutation

Patients with CRR	CaRS-1	CaRS-2	Total
CRR			
No	223 (84.2%)	162 (76.8%)	385 (80.9%)
Yes	42 (15.8%)	49 (23.2%)	91 (19.1%)
Total	265	211	476
G11778A	20 (11.3%)	29 (19.3%)	49 (15.0%)
G3460A	13 (29.5%)	9 (30.0%)	22 (29.7%)
T14484C	6 (19.4%)	11 (35.5%)	17 (27.4%)
Other	3 (23.1%)	-	3 (23.1%)

Abbreviations: CaRS – Case Record Survey; CRR – Complete recovery of response

Table 25. Output from regression analysis (patients)

Effect	Odds Ratio [95% CI]	p-value
G3460A vs G11778A	2.40 [1.32; 4.27]	0.0044
T14484C vs G11778A	2.14 [1.11; 4.00]	0.0232
Age at first symptoms onset	0.97 [0.96; 0.99]	0.0022
Months since first symptoms on	1.00 [0.99; 1.00]	0.0186
Months since most recent sympt	1.00 [0.99; 1.00]	0.0275
Nadir	1.37 [0.80; 2.51]	0.2636

Type 3 Test of Fixed Effects	p-value
Major 3 Mutations	0.0033

Abbreviations: CI – Confidence interval

Two specific genetic mutations, G3460A and T14484C, when compared to the G11778A mutation, show a higher likelihood of influencing the outcome. The odds ratio of 2.40 for G3460A vs. G11778A, with a p-value of 0.0044, and 2.14 for T14484C vs. G11778A, with a p-value of 0.0232, both suggest statistically significant differences. These ratios indicate a roughly 140% and 114% increase in the odds of the outcome for G3460A and T14484C mutations, respectively, compared to G11778A. This highlights the substantial role these specific genetic variations may play in the outcome of interest.

Additionally, age at the first symptom onset appears to have a protective effect, with a decrease in the odds of the outcome as age increases, as shown by an odds ratio of 0.97 and a significant p-value of 0.0022. This suggests that older age at the onset of symptoms is associated with a slightly lower likelihood of the outcome occurring. However, the time since the first and most recent symptom onset presents a more subtle effect, both with an odds ratio of 1.00 and statistically significant p-values of 0.0186 and 0.0275, respectively. This finding indicates a statistically significant, influence of the duration of symptoms on the outcome.

The nadir shows an odds ratio of 1.37, suggesting a 37% increase in the odds of the outcome with an increase in the Nadir value, but this result is not statistically significant, as indicated by the p-value of 0.2636. This lack of significant association suggests that nadir may not be a strong predictor in the context of this study. Overall, these results emphasize the importance of genetic factors, particularly certain mutations, and the age at symptom onset, in influencing the outcome, while the timing of symptoms and nadir appear to have a more limited impact.

Analysis Sets

A13. The EAG notes that there was meaningful heterogeneity between studies in terms of visual acuity at baseline, which may be related to prognosis. As summary statistics may not adequately describe patients baseline VA, especially considering the mixture of off-chart and on-chart patients, please provide an equivalent of Figure 12 from the RHODOS CSR (Visual Acuity at Baseline [ITT population]) for:

- **LEROS ITT population;**
- **EAP LP population;**
- **CaRS I;**
- **CaRS II.**

As noted above, this question has not been responded to.

Study design and patient disposition

A20. Priority question. In Appendix M it is noted that for LEROS, "the natural history control set consisted of data obtained from the case record survey (CaRS) and CaRS II studies". However, it is also stated that "Results from the CaRS II study are not yet available". The EAG notes that the size of the Natural History comparator group (CRS-1 and CRS-2 combined), is large, with N=587 at Day 1 and N=372 considered eligible for matching to LEROS. Please:

a) Clarify how data from the CaRS II study were able to inform the LEROS analysis if the results of CaRS II are not yet available.

b) Provide a breakdown of the number of patients from CaRS I and CaRS II that make up the NH-matched comparator cohort in LEROS.

The disposition of patients who were eligible for the natural history (NH) comparator group are detailed in Table 26. The patient data from the NH control set was further optimised using the matching algorithm for the primary and secondary endpoints. Further details on the matching algorithm used can be found in the LEROS CSR attached to the accompanying reference pack. This resulted in a NH control set consisting of N=106 patients who contributed 193 eyes for evaluation.

Table 26. Breakdown of patients across CaRS studies who were eligible for matched LEROS comparator

	CaRS-1	CaRS-2	Total
Available Case Record Surveys	373	219	592
Age <12 years	12 (3.2%)	6 (2.7%)	18 (3.0%)
No major mtDNA mutations	17 (4.6%)	0 (0.0%)	17 (2.9%)
Unknown year of birth	1 (0.3%)	0 (0.0%)	1 (0.2%)
Eligible subjects	345	213	558
Eligible eyes	690	426	1116
Unknown onset year	21 (3.0%)	8 (1.9%)	29 (2.6%)
Onset of symptoms >5 years	169 (24.5%)	0 (0.0%)	169 (15.1%)

Less than 2 VA assessments, previous idebenone	306 (44.3%)	19 (4.5%)	325 (29.1%)
Eligible patients for matching	168	204	372
Eligible eyes for matching	332	399	731

c) Provide a full written summary of the results of CaRS II, and also provide any study protocol, SAPs and CSRs that are currently available.

CaRS II was an international, multi-centre, historical case record survey which collected data on the VA of eligible LHON patients from existing medical records. The study was conducted in 7 countries (Belgium, France, Germany, Italy, the Netherlands, Poland and the UK) and data from a total of 219 LHON patients and 438 eyes were obtained for this study. The largest number of patients were from Germany, which included 56 (25.6%) of the total patients. This was followed by Poland, which included 40 (18.3%) patients (CSR Table 10.1.1). The remaining patients were distributed across the study sites in Belgium, France, Italy, the Netherlands, and the UK. The majority of study visits (over 50%) from which data were collected occurred since 2010 onwards.

The definitions used for this analysis for characterizing the clinical status of the patients in this cohort, keeping in mind the purpose of using the data as control group in the LEROS study were in line with the ones used in the Raxone clinical development program in RHODOS trial. In that trial, the “best recovery of visual acuity (VA)” was defined as the result from the eye experiencing the most positive improvement in VA from baseline to week 24 using ETDRS charts. The “change in best VA” was measured as the difference between best VA in either the left or right eye at 24 weeks compared to baseline. The clinically relevant recovery of VA from baseline in at least one eye, was defined as either: (i) improvement in VA from unable to read a single letter to able to read at least 5 letters on the ETDRS chart; or (ii) improvement in VA by at least 10 letters on the ETDRS chart.

A total of 219 patients (438 eyes) were included in the full analysis set (FAS) with mean (±SD) observation time of 28.66±44.1 months (range: 0.1 – 196.4 months).

In line with previous literature reports on LHON, the data for this cohort show predominance of disease in males, with only 44 patients (20.1%) being females. The patients reported psychiatric diseases (21.6%) and metabolic diseases (12.2%) as predominant concomitant medical conditions. Also, in line with previous reports on the disease, patients were declaring the symptoms at young age: the mean age at onset of LHON was 29.8 years in the overall study population (±15.0 years; range 6-68 years).

From the perspective of the course of the disease, the study confirms the expected sequence of clinical events in disease progression, with patients reporting either both eyes involved at the same time or a sequential occurrence of symptoms first in one eye and then involvement of the 2nd eye. Sixty-seven (30.6%) patients reported first onset of the disease in the left eye, and 52 (23.7%) patients had first onset of the disease in the right eye. In this cohort, the observed mean (±SD) difference in the time since onset of LHON symptoms between the first and second eye was 2.9±2.4 months (range: 0.1 – 12.0 months). One hundred (45.7%) patients had symptom onset in both eyes at the same time.

The majority of patients in the study had onset of disease symptoms ≤1 year (209 [95.4%]) before baseline. A total of 6 (2.7%) and 4 (1.8%) patients had onset of disease symptoms from >1 to ≤2 years, and >2 to ≤5 years before baseline, respectively (CSR Table 15.2.1).

The predominant mutations reported in LHON were also confirmed by the findings of this cohort: the majority of the study population (157 [71.7%]) had the G11778A mutation. From the 219 total patients, 30 patients (13.7%) had the G3460A mutation and 32 patients (14.6%) had the T14484C mutation.

In the FAS, mean VA for both eyes in patients whose onset of symptoms was ≤1 year before baseline was 0.92±0.64 logMAR. In those whose onset of symptoms was >1 to ≤2 years before baseline this was 1.23±0.60 logMAR, compared to 1.33±0.70 logMAR in those whose onset of symptoms was >2 to ≤5 years before baseline, which confirms

the fast decline and worse clinical prognostic of the disease. Same conclusion was noticed when the progress of the VA was measured taking into consideration best eye VA at baseline. Mean VA measured in the best eye in patients whose onset of symptoms was ≤1 year before baseline was 0.62±0.59logMAR. This was 1.13±0.59 logMAR and 1.30±0.74 logMAR in the best eye of patients whose onset of symptoms was >1 to ≤2 years and >2 to ≤5 years before baseline, respectively (CSR Table 15.3.5,CSR Table 15.3.6).

In the patients with age at onset of the symptoms between 15-35 years, mean VA for both eyes was 0.98±0.66 logMAR. Mean VA measured in the best eye in patients whose onset of symptoms between 15-35 years was 0.64±0.61 logMAR. This study was an historical observational data collection therefore the primary endpoint defined for the analysis of the data was reflecting more a clinically important question and tried less to validate a scientific hypothesis. The evolution of the LHON patients is a clinically important aspect and rare diseases often suffer from limited reported data.

The present study reconfirms the poor diagnostic prognosis of the LHON patients. Of the 96 eyes which had a 12 month VA assessment post-BL, 20 had an evolution matching the definition of clinical relevant benefit (CRB) (CSR Table 11.5.1), which corresponds to a responder rate of 20.8%.

As the definition includes patients reporting stabilization and as this is defined not as maintenance of the VA, but rather not evolving into the blindness category, the number of those who truly improved at 12 months (clinical relevant recovery, CRR) was even lower, as from these 20 eyes with CRB, 8 had a CRS but not a CRR (CSR Table 11.7.3). Twelve eyes (12.5%) had a CRR with a median gain of 30 letters in the ETDRS chart.

The age group with highest percentage of benefit at 12 months was patients with < 15 years old and T14484C carriers. The T14484C carriers had also the best VA reported at baseline versus G11778A or G3460A.

Most of the data analysed came from patients with ≤ 1 year since symptoms onset at Baseline. Of the 96 eyes which had a 12 month visit post-BL, 12 (12.5%) had a CRR

of 155 with a median gain of 30 letters in the ETDRS chart (ranging from 15 to 65 letters in ETDRS chart).

Data on VA at 12 months in eyes of patients with baseline within > 1 year since symptoms onset was only available in a very limited number of eyes/patients: 11 eyes from 10 patients who were all older than 15 years old at symptoms onset and who had G11778A (9 eyes) and G3460A (2 eyes) mutations. In these patients, overall CRB was reported in 36.4% eyes (4 out of 11 eyes) which were analysed for VA at 12 months after baseline. CRB was only observed in patients who were between 15 and 35 years old at symptom onset (44.4%) and carriers of G11778A (50.0%).

Within the limits of evidence generated out of a retrospective observational cohort, the study provided information on the VA of patients on a yearly basis, for patients observed for more than 5 years. While data was not available for the same patients at each of these time point assessments, those analysed for VA status at 5 years since baseline out of the total patients (37 patients) for whom data was provided at more than 5 years follow-up, 35.1% (13 patients) had Best VA off-chart.

Overall, the retrospective data collected and reported in the CaRSII study brings important confirmatory information on the evolution and builds on the evidence and knowledge on LHON as a rare disease.

A22. The main secondary outcome in the RHODOS trial: change from baseline in patients' best VA, considered the most relevant for clinical practice in the CS, compared patients' better seeing eye at baseline with the VA in patients' better seeing eye at week 24 even if the better-seeing eye at week 24 was not the same as the better-seeing eye at baseline. Please provide the number of participants in each group whose best seeing eye changed from one to the other between baseline and follow-up. Please provide this data for participants across studies (EAP, LEROS, CaRS I and II) if available.

As noted above, this question has not been responded to.

HRQoL

A24. From RHODOS, please provide a scatterplot of patients' VF-14 against the best VA at each time point.

As noted above, this question has not been responded to.

A25. From RHODOS, please provide the results of a mixed-effects model predicting VF-14 with the best VA (fixed effect), treatment (fixed effect) and patient ID (random effect). If deemed appropriate, please also include the visit and the interaction of treatment by visit in the model.

As noted above, this question has not been responded to.

Subgroup Data

A27. Priority. The EAG's clinical experts noted it is plausible that the benefit a patient may receive from idebenone treatment may be largest if they are treated prior to nadir, but noted the lack of available data to support this. The EAG notes that the company subgroup analyses of patients <1 year since symptom onset vs >1 year since symptom onset do not suggest an interaction between treatment and time since symptom onset, but the EAG notes that:

a) **The clinical trials were not powered to detect subgroup effects, and;**

b) **Dichotomising patients around 1 year since symptom onset is unlikely to be a powerful test of the interaction between time since onset and treatment effect, as time since onset is a continuous predictor that may have a non-linear relationship with treatment effect.**

Please:

c) **Comment on whether the Company believes the clinical and cost-effectiveness of idebenone may be larger in a subgroup of patients**

treated either early on in the disease course, or with a baseline logMAR < 1.

Considerations regarding rationale for the division of time since onset < 1 year and > 1 year in the management/ research of LHON.

Prior to the conduct of clinical trials utilising idebenone in LHON (RHODOS, EAP), it was widely held that retinal ganglion cells would lose functionality 12 months post onset, with limited possibility of recovery, if any. Furthermore, experts asserted that once the disease had progressed beyond the 5-year onset threshold, there were no chances of recuperation.

It had been suggested empirically that the best time for therapeutic intervention is during the first weeks/months of development after the onset of symptoms.

The RHODOS study was specifically designed with this objective in mind for the aforementioned reasons.

In the RHODOS study, the main aim was initially to establish if the administration of idebenone to patients with LHON onset within the last three months could alleviate visual loss in the least affected eye. The primary endpoint was to determine the percentage of patients in whom the initially least affected eye did not deteriorate to more than 1.0 logMAR by Week 36. Participants were mandated to present with the eye having the worst VA affected >0.5 logMAR and the eye that was least affected <0.4 logMAR at baseline to uphold a noteworthy variation in VA between their eyes, where the natural history would entail a high probability of decline in the least affected eye during the study duration. Meeting these criteria was proving to be extremely challenging, as no patients meeting the inclusion criterion with one affected eye and one unaffected eye had been randomized into the trial 12 months after initiation. Therefore, the protocol was revised, and modifications were made to the primary objective and endpoint to enhance recruitment. The criterion for the onset of visual impairment within 3 months of Baseline was extended to include established disease of 5 years or less prior to Baseline (stratification for > and ≤ 1 year was introduced), and the exclusion of patients with VA worse than 0.4 logMAR in the least affected eye was correspondingly removed.

After the results of RHODOS, including the post-hoc analyses agreed with EMA, were reported, it became clear that eyes/patients could show a therapeutic benefit with idebenone even after 12 months from disease onset. Additionally, the post-hoc analyses demonstrated that the clinically relevant recovery (CRR) response was not restricted to eyes with less than a year since onset or those with already off-chart visual acuity at baseline.Although it failed to achieve the primary endpoint, RHODOS afforded valuable perspectives on drug study design. To derive pertinent conclusions, we must take into account:

- Endpoints (including both recovery and prevention of deterioration),
- Time to evaluation of endpoints (with 6 months being inadequate to discern treatment benefits), as well as
- Time since onset at baseline (indicating that eyes may still benefit from therapy even after 12 months [but less than 5 years] since onset).

Future trials should consider a lengthier treatment period, endpoints targeted at avoiding deterioration and/or promoting recovery, and disease progression at baseline not limited to less than one year since onset, or degree of visual acuity.

A real-world evidence study, of an uncontrolled and retrospective nature, namely the Expanded Access Programme (EAP), gave further evidence of the potential evolution and benefit of longer-term idebenone treatment. The EAP compiled data from patients treated with idebenone for longer periods (over two and even up to five years) who had shown the onset of symptoms less than 12 months before treatment.

The findings present additional knowledge on the capabilities and potential of idebenone, contributing to the enhancement of clinical management of LHON and the design of potential new trials.

Despite knowledge that untreated LHON patients undergo a reduction in visual function to various degrees of visual acuity (nadir), the EAP demonstrated that idebenone did not necessarily prevent this nadir in some cases. Interestingly, though, many of these eyes/patients exhibited further recovery of visual acuity to clinically relevant levels when treatment was continued beyond this observation point. This

improvement might require several months of continued therapy. This "nadir" on therapy is acknowledged at present, though no explanation has been found.

An additional outcome of this observation is the inclusion of an efficacy parameter that allows for the evaluation of effectiveness based on both the value of VA at nadir and the baseline (namely, CRR from nadir and CRR from baseline, respectively).

Another finding from the EAP is that patients who begin therapy prior to 12 months since onset (regardless of the degree of VA loss or timing of treatment initiation) may require up to 24 months to demonstrate a CRR. Additionally, it has been observed that with continued therapy, the extent of visual acuity recovery may increase even beyond the threshold of CRR, with maintained therapy.

So far, it is not known what factors determine the time to or degree of the nadir on therapy or the potential response (and time to it) to therapy.

In 2016, a group of experts reached consensus on different aspects of the knowledge and management of LHON, which are relevant to the current discussion.

Of note, they divide the course of the natural history of LHON into 4 stages or phases:

- Asymptomatic (before symptoms onset)
- Subacute: approximately first six months after symptoms onset.
- Dynamic: approximately from 6 to 12 months.
- Chronic: from 12 months since onset, onwards

The occurrence of nadir in the natural history of untreated patients usually takes place during the first 12 months since onset. It can happen, however, even after this time.

For this reason, LEROS was designed as a long-term therapeutic study on subjects either in the subacute-dynamic or chronic phase.

The results of LEROS do not indicate that the response is of different direction or magnitude if patients are treated in the different phases of the disease, as CRR, CRS,

CRW or CRB can still be observed in any of them. There is no evidence pointing at a treatment benefit if therapy is started before 12 or after 12 months since onset. There is no evidence, either, that the benefit of therapy is restricted to a VA better than 1.0 logMAR (or even that patients cannot benefit from therapy if the eye is already off-chart).

Therapeutic objectives can depend on the phase of the disease.

In the subacute/dynamic phase of the disease, when most of the VA deterioration takes place, prevention, in the form of CRS (clinically relevant stabilization) if the VA is still better than 1.0 logMAR, or prevention of CRW (clinically relevant worsening) if the VA is between 0 and 1.6 logMAR, are the desirable ones. Although clinically relevant recovery (CRR) is always desirable, at these stages, might not always be realistic or achievable.

In the chronic phase of the disease, most of the VA deterioration has taken place, recovery, in the form of CRR (clinically relevant recovery) is the desirable objective. In those case that VA is still better than 1.0 logMAR, clinically relevant stabilization would also be desirable.

Specifically in relation to the request to comment on "whether the Company believes the clinical and cost-effectiveness of idebenone may be larger in a subgroup of patients treated either early on in the disease course, or with a baseline logMAR < 1."

The company does not believe that results (be them clinical or cost-effectiveness) will be larger in patients treated earlier or with a baseline VA better than 1.0 logMAR.

From the data exposed previously, idebenone has shown benefit in patients who started therapy either during the subacute/dynamic phase or chronic phase. In a disease where the natural history of untreated eyes is towards a severe and permanent loss of visual function, any prevention of further deterioration and/or recovery of lost vision, has an important positive benefit for the patient.

The current opinion of the experts that developed the Consensus in 2016, currently consider that patients should be treated as soon as they are diagnosed, independent

of the phase (subacute/dynamic or chronic) and the degree of visual function loss. They also consider that minimum treatment duration before considering the treatment a failure, should not be less than 24 months.

The above is an attempt to describe the challenge in answering the question posed. The results from RHODOS, EAP & LEROS describe a reasonably consistent response to idebenone therapy in all phases of the evolution of symptoms & across different mutations. The company believe that the overwhelming evidence from clinical trials & routine practice is that idebenone should be available as an option to all LHON cases regardless of visual acuity or time from symptom onset.

d) **Provide the following scatterplots for RHODOS, LEROS and the EAP patients:**

- **Baseline best logMAR vs Last visit best logMAR;**
- **Time since symptom onset vs Last visit best logMAR.**

Please include separate graphs for idebenone treated patients (RHODOS, LEROS and EAP), placebo treated patients (RHODOS) and propensity score matched/weighted controls (LEROS).

As noted above, this question has not been responded to.

e) **Please provide appropriate regression analyses between: i) baseline logMAR and last visit best logMAR, and ii) time since symptom onset and last visit best logMAR for RHODOS and LEROS (propensity score matched analyses). For the time since symptom onset analysis, please consider using a non-linear model structure.**

As noted above, this question has not been responded to.

Individual Participant Trajectories

A28. Priority question. The EAG is concerned that the individual patient trajectories implied by using a Markov model might not reflect the individual patient trajectories observed in clinical trials, but notes these data have not

been provided. Please provide the following graph by visit for patients in RHODOS idebenone and placebo patients (including OFU visit), EAP idebenone patients and LEROS idebenone and matched-control patients. Please use a transparency value for the individual lines that overlap.

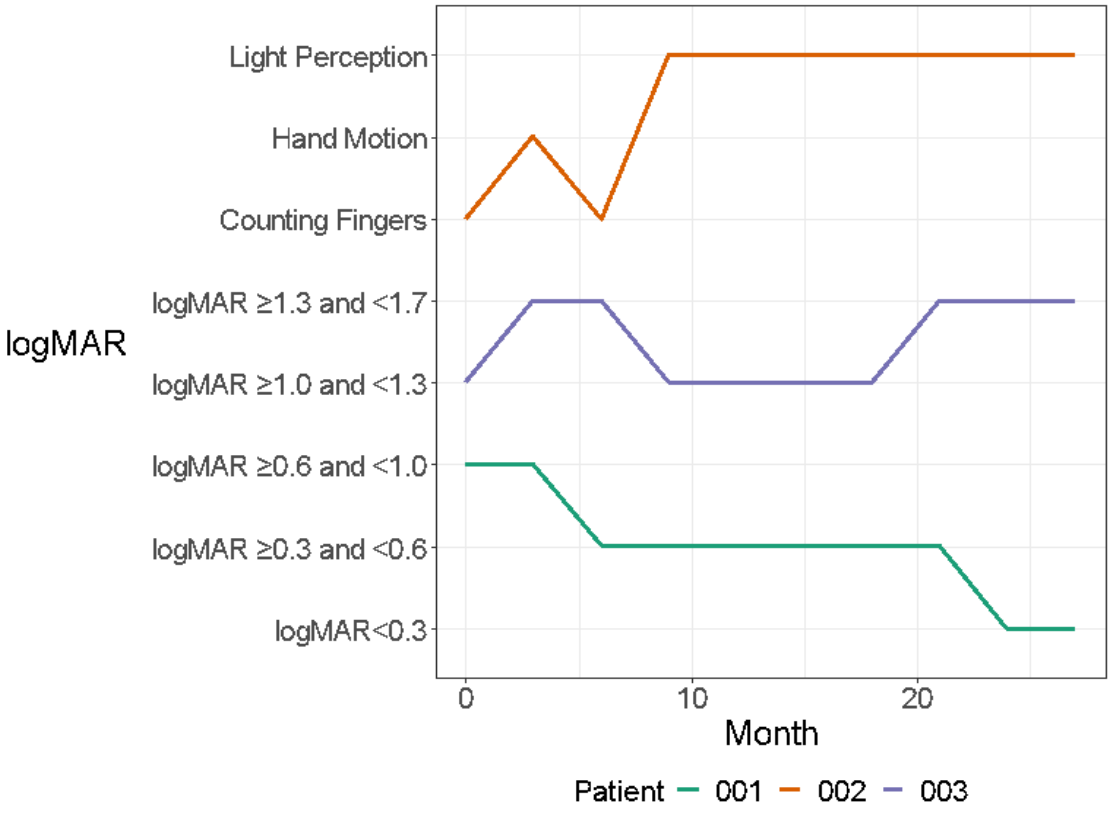


Figure 3. Patient trajectories for RHODOS idebenone arm including OFU

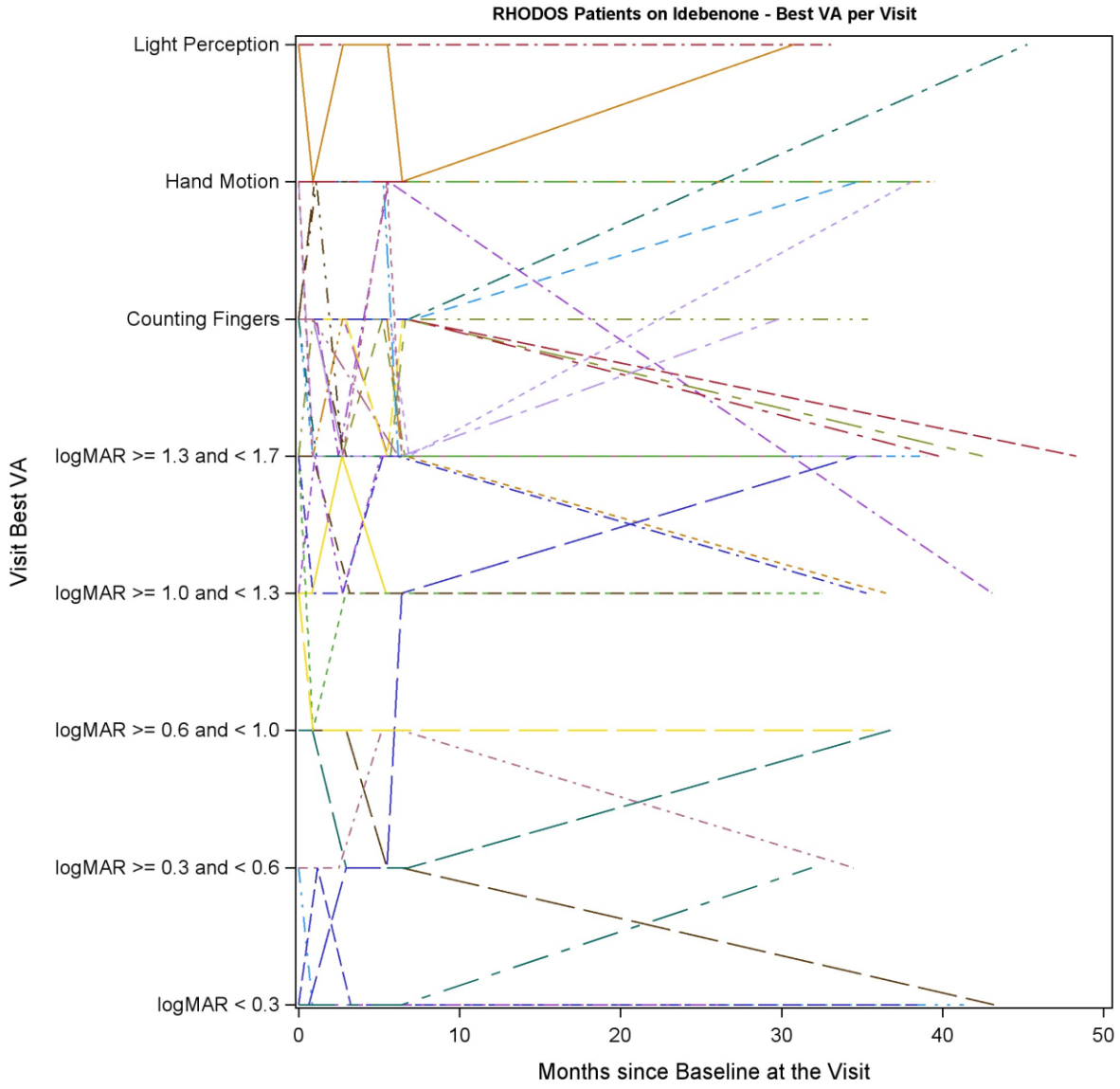


Figure 4. Patient trajectories for RHODOS placebo arm including OFU

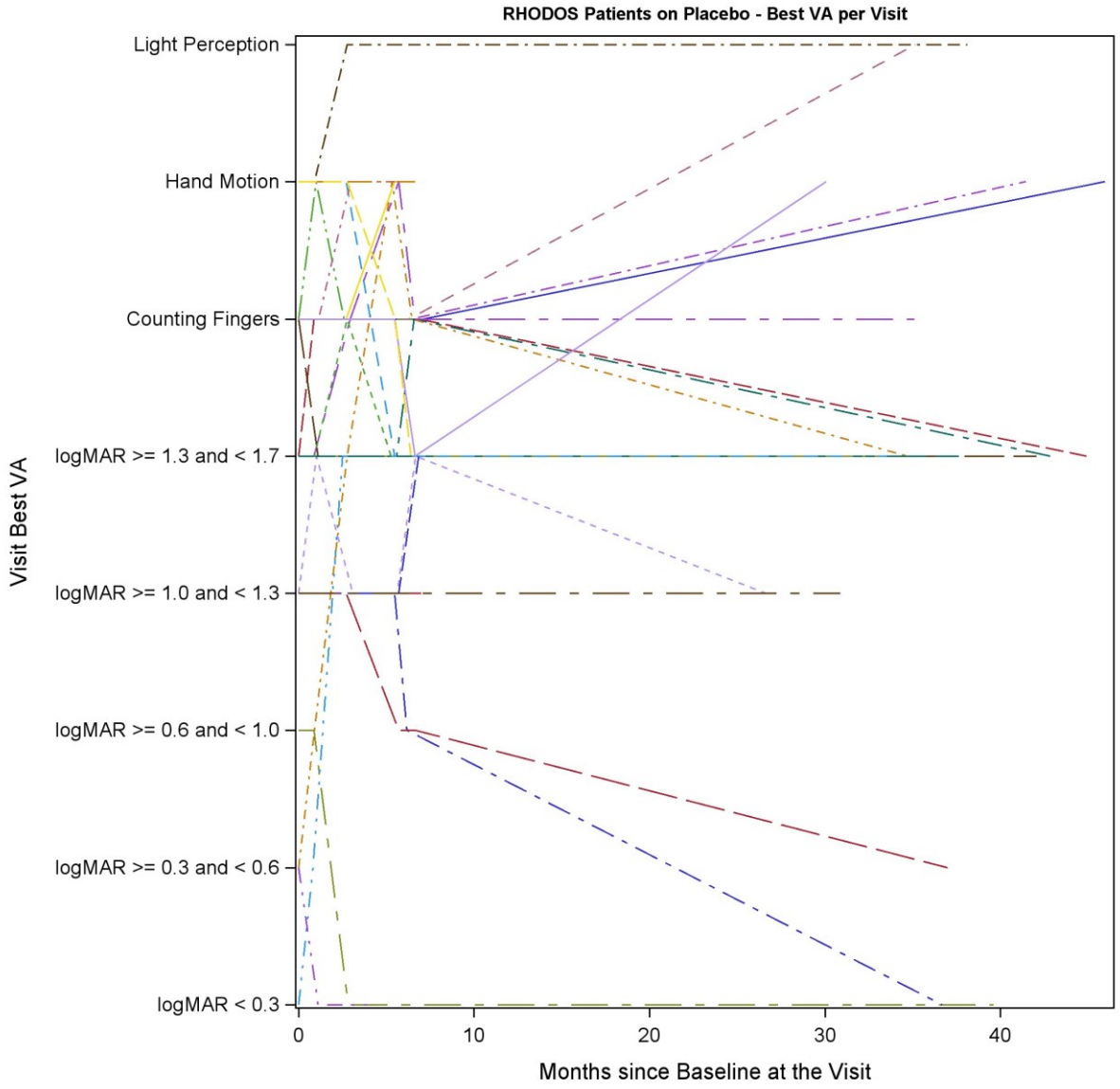


Figure 5. Patient trajectories for EAP idebenone arm

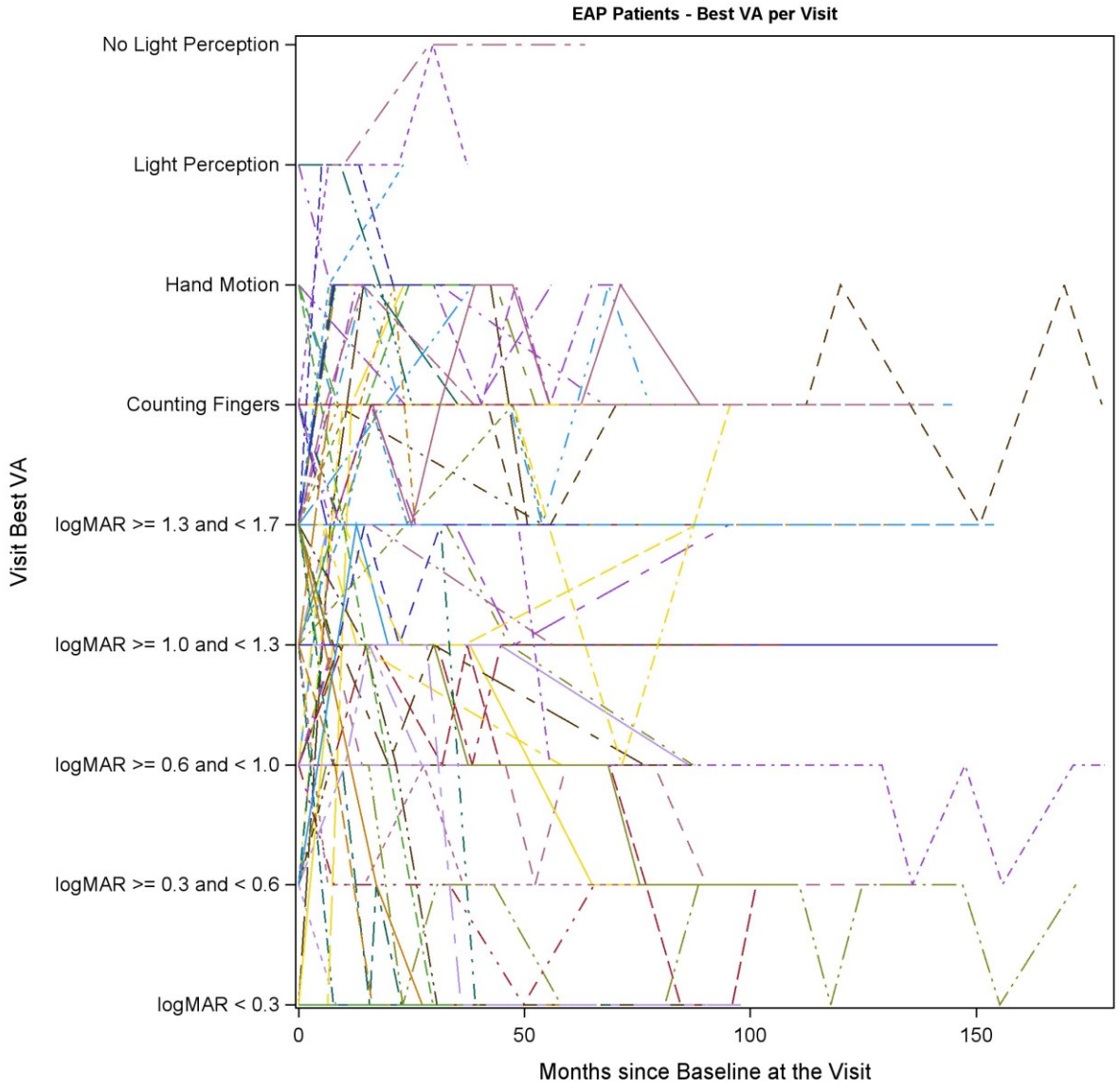


Figure 6. Patient trajectories for LEROS idebenone arm

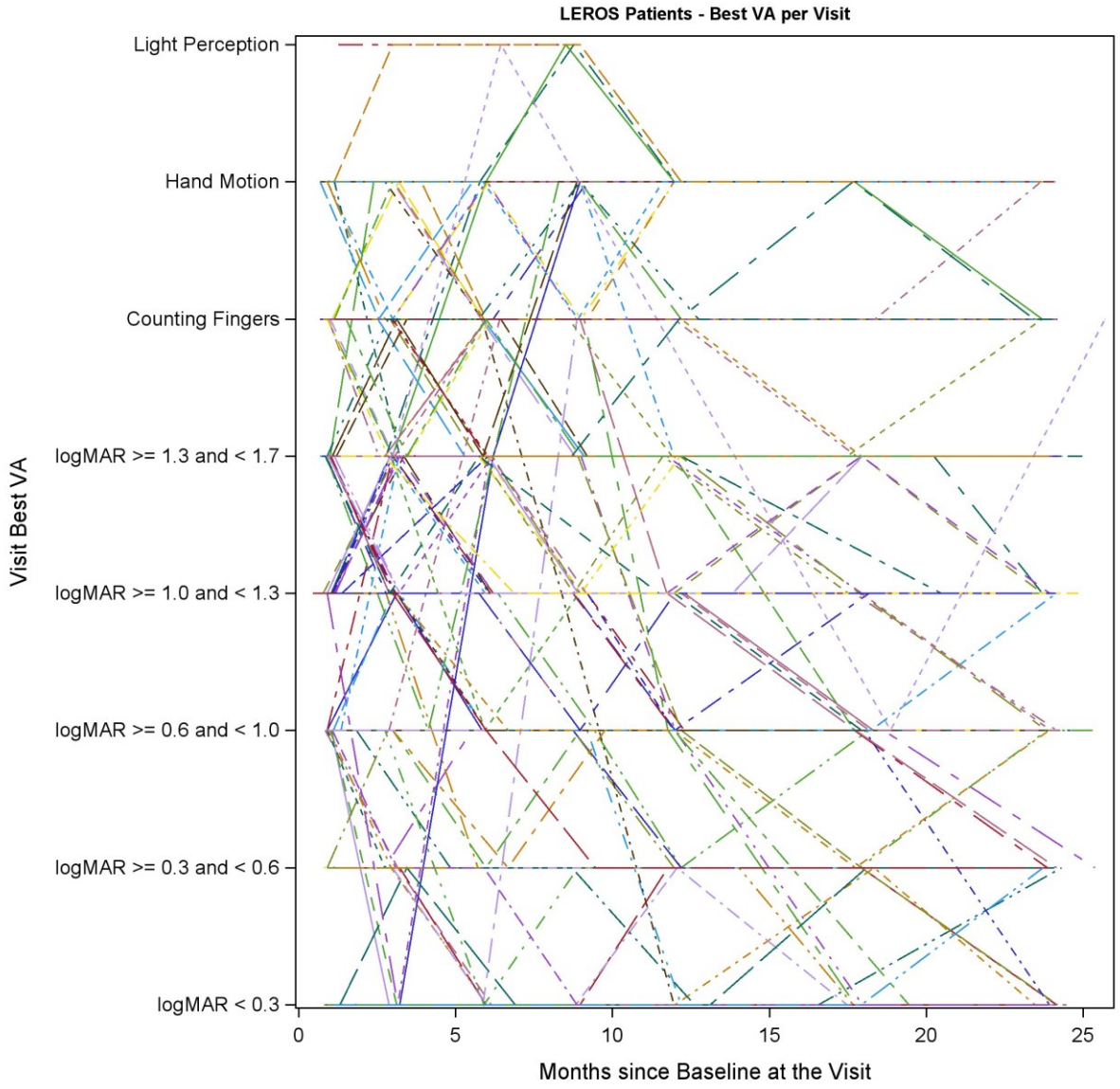
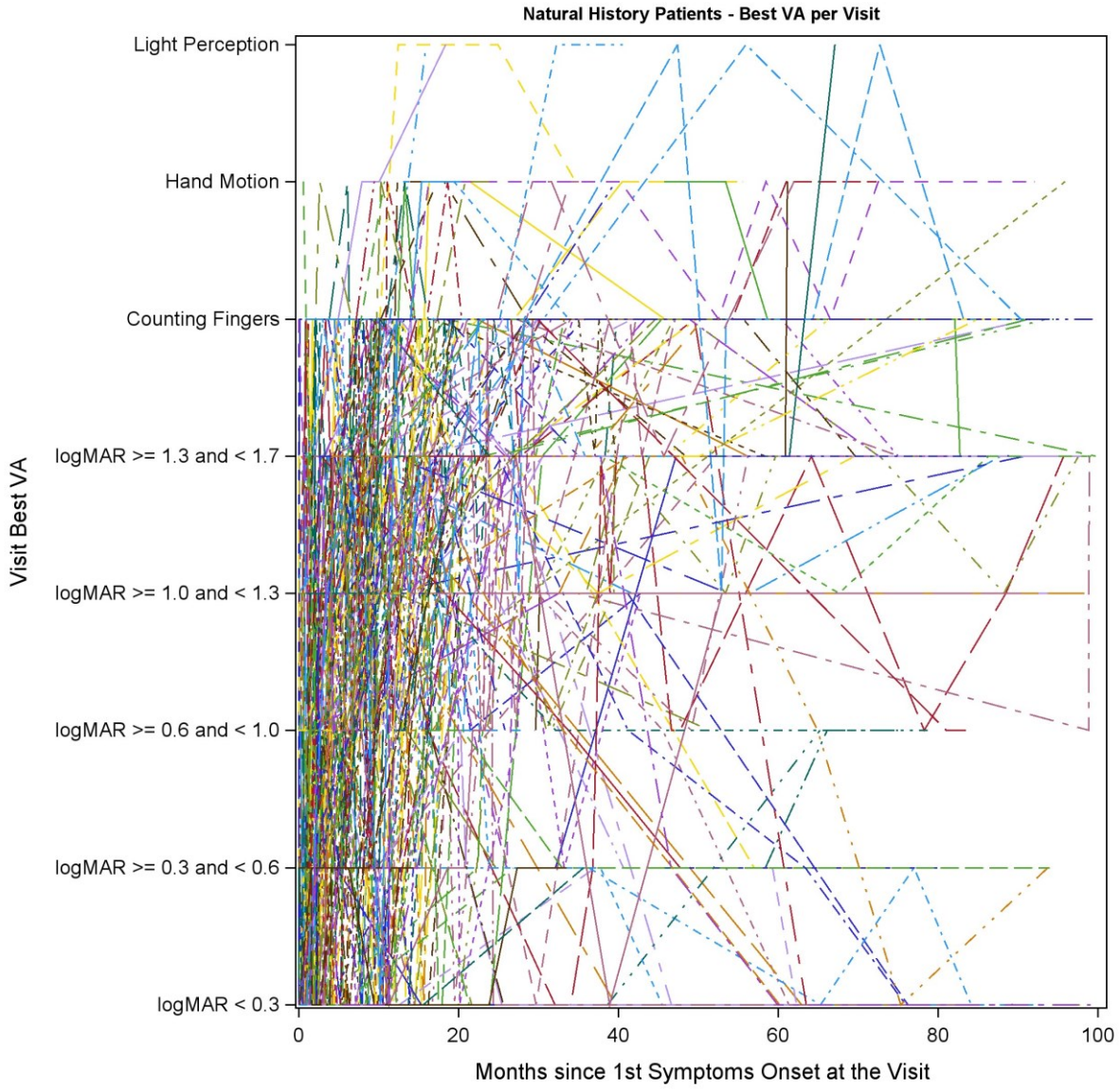


Figure 7. Patient trajectories for LEROS matched control arm



A29. Priority question. Please complete the following tables for: i) RHODOS idebenone patients (including OFU visit); ii) RHODOS placebo patients (excluding OFU visit); iii) RHODOS idebenone patients (including OFU visit); v) EAP idebenone patients; vi) LEROS idebenone patients; vii) LEROS matched-control patients and vii) CaRS patients.

a) Change in logMAR from baseline

	LogMAR at final visit

		<0.3	≥0.3 and < 0.6	≥0.6 and < 1.0	≥1.0 and < 1.3	≥1.3 and < 1.7	Hand Motion	Counting Fingers	Light Perception
LogMAR at baseline	<0.3								
	≥0.3 and < 0.6								
	≥0.6 and < 1.0								
	≥1.0 and < 1.3								
	≥1.3 and < 1.7								
	Hand Motion								
	Counting Fingers								
	Light Perception								

b) Change in logMAR from nadir

		LogMAR at final visit							
		<0.3	≥0.3 and < 0.6	≥0.6 and < 1.0	≥1.0 and < 1.3	≥1.3 and < 1.7	Hand Motion	Counting Fingers	Light Perception
	<0.3								
	≥0.3 and < 0.6								
	≥0.6 and < 1.0								
	≥1.0 and < 1.3								

LogMAR at nadir	≥1.3 and < 1.7								
	Hand Motion								
	Counting Fingers								
	Light Perception								

As noted above, this question has not been responded to.

Section B: Clarification on cost-effectiveness questions

B19. As noted in question A20, and confirmed in the unpublished LEROS manuscript, data from CaRS II appears to be available but has not been included in the economic model.

a) Please provide a scenario analysis using the combined CaRS I and II datasets for the SoC arm in the economic model;

The company would like to highlight that a patient count analysis had not been performed using the CaRS II data at the time of submission. As part of the company's response to this clarification stage, a post-hoc analysis of the CaRS II data has been performed in which patients treated with idebenone have been removed from the dataset and pooled CaRS I and CaRS II patient counts have been derived.

Please see the company's response to Question B21 for the results of the scenario analysis using pooled CaRS I and CaRS II datasets to inform the SoC arm.

b) If it is not possible to pool the studies please explain why pooling would be inappropriate and provide a scenario analysis using the treatment effect measured in CaRS II for the SoC arm in the model;

A scenario using pooled data from CaRS I and CaRS II has been provided in response to Question B21.

c) If the company considers the results of CaRS II to be unavailable, despite their use in the LEROS analysis, please outline when the full results of CaRS II will be available?

A scenario using pooled data from CaRS I and CaRS II has been provided in response to Question B21.

B20. Priority question. The EAG thanks the company for providing a scenario using the EAG's preferred model structure as outlined in EAG clarification B1. The EAG notes, however, that the LEROS patient data is unable to be used in the proposed model structure. Please can the company provide a justification

for why this functionality was not built into the model and additionally conduct a scenario using the EAG's preferred model structure and LEROS patient data.

As detailed in the company's response to Question B1 of the original clarification questions ("*ID547 idebenone clarification letter to PM for company CON_Responses_28Nov23*"), the company strongly consider the base case model to be adequately robust and clinically and economically plausible for decision making in patients with LHON. The company's response to Question B1 details how the current model structure:

- Robustly captures the natural progression of LHON over time by accounting for the significant differences in QoL and resource use, as detailed in literature and by clinical experts, across small and varying LogMAR ranges.(1)
- Has been extensively validated by clinical experts in LHON and HTA bodies worldwide and uncertainty has been adequately explored through deterministic, probabilistic and scenario analyses.
- Aligns with previous NICE TAs which assess VA in similar logMAR ranges TA274, TA283 and TA298. (2–4)
- Differs from the model structure used in HST 11 due to the differences in the modelled population and distribution of patients.

Even modest changes in VA can make a meaningful difference to patients such as being able to recognise who has walked into a room rather than just knowing that someone has or being able to read a clock to tell the time. Therefore, the company strongly considers that the current model structure should be used in this base case CEA for modelling idebenone for treating LHON patients as it is the most appropriate for decision making. The EAGs proposed health states are inappropriate as they do not adequately or robustly capture the differences in QoL and the cost-savings demonstrated across the small LogMAR ranges.

However, the company have explored a scenario adopting the EAG's proposed health states using LEROS patient data. As described in the company response to question B1, a scenario to explore the impact of a simplified model structure using the EAGs preferred health states has been implemented into the current model structure. The scenario uses the same average utilities and resource use for the health states that

have been pooled and adjusts patient counts by pooling counts from the grouped health states and applying them the aggregated health states. Further detail on how the scenario has been implemented is detailed below.

Clinical data

Patient counts were summed together for each proposed health state for each cycle in each treatment arm. Please see the Table 17, response to B1, in "ID547 idebenone clarification letter to PM for company CON_Responses_28Nov23" which demonstrates the calculations conducted to obtain patient counts for the aggregated health states: patient counts in each yellow rectangle that were summed together and then assigned to aggregated health states in the company's model, using the patients counts from baseline to month 3 in the idebenone arm as an example. Patient counts for the idebenone arm were informed using RHODOS from baseline to month 3 and LEROS from month 6 to month 24 and patient counts for the SoC arm were informed using RHODOS from baseline to month 3 and CaRS from month 6 to month 36.

HRQoL

Please see the response to B1, in "*ID547 idebenone clarification letter to PM for company CON_Responses_28Nov23*" for the approach to group health state utility values.

Resource use

Please see the response to B1, in "*ID547 idebenone clarification letter to PM for company CON_Responses_28Nov23*" for the approach to group health state resource use.

Results

The deterministic scenario results using the EAG's proposed health states with LEROS data for idebenone from 6 months vs SoC are presented in Table 20. This has led to an increase in the new company base case ICER of £8,040, from £18,758 to £26,798. This is also an increase in ICER from the scenario using the base case model structure with the LEROS data (£21,129). This scenario resulted in an ICER that is still

below the cost-effectiveness threshold of £30,000. However, due to the clinically implausible grouping of health states, this scenario does not accurately capture the QoL and cost burden of LHON across varying LogMAR ranges, and therefore, this ICER is not a true representation of the cost-effectiveness of idebenone.

Table 20: Deterministic scenario results using the EAG's proposed health states with LEROS data (PAS price)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
SoC	[redacted]	[redacted]	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	26,798

Abbreviations: ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life-years; SoC – Standard of care

B21. Priority question. The EAG thanks the company for clarifying the observations generated using LOCF in EAG clarification question B3. The EAG notes that 774 VA observations were taken from the 74 natural history outcomes patients in CRS-1 and that CRS-2 recorded observations from 219 natural history patients. Please can the company explain what data from CRS-1 and -2 is being used to inform the SoC transition probabilities given the breadth of data available from the studies and from year one in the model onwards more than 80% of the observations used to calculate SoC transition probabilities are generated using LOCF (96% by year three). As a scenario, please calculate the transition probabilities for SoC patients in the model using the combined VA patient observations from CRS-1 and -2. Additionally, please allow this scenario to be conducted using the EAGs preferred model structure.

The SoC transition probabilities in the model are solely derived from CaRS I, as this was the only data available with idebenone naïve patients. As detailed in the company response to Question B19 above, as part of the company's response to the clarification stage of this appraisal, a post-hoc analysis of the CaRS II data has been

performed in which patients treated with idebenone have been removed from the dataset.

As a scenario, the company have derived patient counts using the pooled CaRS I and CaRS II data and applied them to the EAGs preferred model structure. Only VA assessments from patients who had not received idebenone post-baseline were included. The methodology for deriving patient counts aligns to the approach used to derive patient counts for the CaRS I only data, as detailed in Section B.3.3.2.2 of the company submission (CS). The company understand that the EAG wish to pool together the CaRS I and CaRS II datasets to mitigate the need for using LOCF in the SoC arm. Therefore, no LOCF approach is applied to the pooled CaRS I and CaRS II patient counts. Please note that given this is natural history data in an ultra-rare disease, recorded observations in the long-term follow-up still remain limited, even with the pooled data sets. Patients need consecutive observations at each timepoint in order to be included in patient counts per cycle. Since there are limited patients with consecutive observations, data are limited.

To view this scenario, please set 'Settings G29' to "Yes", and then 'Clinical Inputs Q15' to "RHODOS/CRS I/CRS II (no LOCF)". The deterministic scenario results using the pooled CaRS I and CaRS II data from 6 months onwards in the SoC arm with the EAGs preferred health states are presented in Table 27. This has led to a decrease in the new company base case ICER of £12,295, from £18,758 to £6,463. This scenario resulted in an ICER that is below the cost-effectiveness threshold of £30,000.

Table 27: Deterministic scenario results using the pooled CaRS I and CaRS II dataset with the EAG's proposed health states (PAS price)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
SoC	[redacted]	[redacted]	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	6,463

Abbreviations: ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life-years; SoC – Standard

B22. Priority question. With respect to EAG clarification question B4, the company has accidentally misinterpreted the question. The EAG requested

that the SoC transition probabilities be made probabilistic, similar to the idebenone transition probabilities; however, instead the company has removed the probabilistic capability of the idebenone transition probabilities. Please update the model so that both idebenone and SoC transition probabilities can be made probabilistic and usable for PSAs. Given the uncertainty in treatment effects for both idebenone and SoC, and the NICE reference case stipulating the importance of probabilistic results for use in committee decision making, the EAG is currently unable to provide probabilistic results which incorporate uncertainty related to the treatment effect and so it is likely that any results provided will not be suitable for decision making.

As detailed in the company's response to Question B4 of the original clarification questions in *"ID547 idebenone clarification letter to PM for company CON_Responses_28Nov23",* due to the ultra-rarity of LHON and resulting low patient numbers, including the transition probabilities in the probabilistic sensitivity analyses (PSA) creates substantial uncertainty in the probabilistic results of the CEA. Therefore, the transition probabilities have not been included in the PSA.

The transition probabilities model the natural disease progression of patients treated and not treated with idebenone and are based on clinical trial data, which are the most robust and reliable source available. Given the low patient numbers, even small variations in patient counts would significantly alter the clinical effectiveness and disease progression being modelled in both treatment arms in the CEA. Therefore, the company strongly considers that including the transition probabilities in the PSA will create highly inaccurate probabilistic cost-effectiveness results that will be inappropriate for decision-making.

However, in order to explore some uncertainty in the clinical data, the company have already included the baseline distribution of patients in the PSA which varies the number of patients starting in each health state which is a natural variation in clinical practice.

B23. With respect to EAG clarification A2, the EAG would like to clarify the request for a scenario analysis using the matched patient population identified

in part a) of question A2 in the economic model (matcher or weighted analysis of the full LEROS ITT population and full CRS data set [studies I and II]).

Results from the matched or weighted analysis of the full LEROS ITT and full CaRS study cannot be used to inform transition probabilities for idebenone and SoC, respectively. As described in responses to B2, the Natural History matched controlled comparator cannot be used to inform transition probabilities for SoC in the economic model due to the matching algorithm being performed de novo at each time point. Even when reperforming the matching algorithm for individual patients as per the request for A2, the per cycle transition counts cannot be derived as the same patient will not be followed over the trial duration and therefore, their movement across health states cannot be accurately captured. Given this, the CaRS I study has been utilised to inform the SoC arm of the model beyond six months.

B24. The EAG notes that although there were 53 patients in the idebenone treated arm of the RHODOS ITT population, only 50 patient observations are used to calculate the idebenone RHODOS derived transition probabilities. As a scenario please use the full RHODOS ITT population to inform the idebenone transition probabilities. Additionally, 29 patients were in the SoC arm of the RHODOS trial however 30 patient observations are used to calculate the SoC transition probabilities. The EAG assumes the additional observation is imputed to allow patients to remain in their previous health state. Please can the company confirm this assumption.

The EAG is correct to note that 50 patient observations are used in the idebenone patient counts from Baseline to Month 3, using data from the RHODOS ITT population. This is due to the [redacted] as detailed in response to question A10 in "ID547 idebenone clarification letter to PM for company CON_Responses_28Nov23". A further sensitivity analysis was performed for the whole ITT population including data from the three randomised patients who were prospectively excluded from the ITT population. Results seen (Table 6, A10) were similar to those for the ITT population. At Week 24, the estimated mean treatment

difference between idebenone and placebo was logMAR -0.098 (equivalent to 4 letters), 95% CI: logMAR -0.230, 0.034, p=0.144.

Due to the small number of patient exclusions (<6%) and similar results across the ITT cohorts, transition probabilities for the full ITT set (53 patients) were not derived, as their omission is unlikely to significantly impact the overall cost-effectiveness results.

The company can confirm that the SoC additional observation is imputed to allow patients to remain in their previous health state. As discussed in Document B, Section 3.3.2.2, there are instances where no data was collected to inform a transition from one health state to the seven health states. Where this is the case, it was assumed that the patient remained in the same health state. This was the case for the SoC arm, cycle 1, LP to LP.

References

1. Brown GC. Vision and quality-of-life. Trans Am Ophthalmol Soc [Internet]. 1999 [cited 2023 Jun 1]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1298275/

2. NICE. Ranibizumab for treating diabetic macular oedema | Guidance | TA274 [Internet]. NICE; 2013 [cited 2023 Sep 18]. Available from: https://www.nice.org.uk/guidance/ta274

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4. NICE. Ranibizumab for treating choroidal neovascularisation associated with pathological myopia. TA298. 2013.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	**Leber's Hereditary Optic Neuropathy Society (LHON Society)**
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are a patient-led support group for a rare condition called Leber's Hereditary Optic Neuropathy (LHON). Our group is comprised of LHON patients, family members, and medical professionals. We are a registered charity with the Charity Commission (number 1157206) for England and Wales. **Our aims** • To provide support and information to those impacted by LHON; patients, their family, friends, and healthcare providers. • Provide guidance and representation on issues that affect the LHON community. • Promote up-to-date knowledge and understanding of LHON in the welfare, medical and scientific communities. • Facilitate research into understanding and seeking ways of preventing and ultimately reversing sight loss in LHON affected patients. **Our funders** The LHON Society is a charitable organisation funded by government initiatives and private fundraising activity.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months?	No

[Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Through social media and patient interviews

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with Leber's Hereditary Optic Neuropathy (LHON) can present significant challenges as it is a rare genetic disorder that primarily affects vision. Individuals with LHON may experience devastating, rapid onset of vision loss, most people meet the legal criteria for blindness within 1 year, and the majority remain chronically visually impaired without any spontaneous improvement (Carelli, 2017) Here are some aspects of what it's like to live with LHON: • Vision Loss: LHON typically causes a rapid loss of central vision in both eyes, often leading to severe impairment or legal blindness. This loss can be sudden and unpredictable, occurring over days, weeks, or months. This sudden change often leads to several misdiagnoses and to a long period of time without any diagnosis. “My vision loss happened over 2 weeks, I could see perfectly well and then, I couldn’t. It was devastating. I couldn’t do my job, my whole life was turned upside down” • Central Vision Impairment: Individuals with LHON often retain their peripheral vision, but their central vision, which is crucial for tasks such as reading, driving, and recognizing faces, is severely affected. This can significantly impact daily activities and independence. Added to this peripheral vision can lose clarity and colour perception. “It’s frustrating, every daily activity has changed. I use assistive technology to help me get dressed. We needed to change our plates so I could find food. If I’m lucky enough to become a parent, I’ll never see my children’s faces”. • Progression: The progression of vision loss in LHON can vary among individuals. Some people may experience a sudden onset of symptoms, while others may have a more gradual decline. In some cases, vision loss may stabilise after initial deterioration. • Emotional Impact: Coping with the loss of vision can be emotionally challenging. Individuals with LHON may experience feelings of grief, frustration, anxiety, and depression as they adjust to their changed circumstances and navigate the practical challenges of daily life. • Adaptive Strategies: Learning to adapt to life with vision loss is essential for individuals with LHON. They may need to rely on assistive technologies, such as screen readers, magnifiers, or speech-to-text

	software, to access digital information. Orientation and mobility training can also help individuals navigate their surroundings safely. • Treatment Options: people living in England have no access to treatment. In Wales and Scotland, the NHS provide active treatment with Idebenone. • Lifestyle Adjustments: Living with LHON often requires making significant lifestyle adjustments to accommodate vision loss. This may include modifying home environments for accessibility, using alternative transportation methods, and adapting leisure activities and hobbies to suit visual limitations. A qualitative exploration of how Leber Hereditary Optic Neuropathy affects patients and their relatives' quality of life (Chen, 2022), reported respondents expressed profound distress upon receiving the LHON diagnosis following a prolonged and anxiety-inducing diagnostic process. Patients found themselves devasted by the loss of independence, a struggle that extended to their family members. They recounted encountering difficulties in various aspects of life, encompassing physical abilities, emotional stability, interpersonal connections, professional and educational pursuits, financial matters, and leisure activities. Disparities in access to disability benefits, visual aids, and subsidised Idebenone across different countries led to unequal financial burdens. There is optimism among patients for treatments that could restore independence and enhance their capacity to lead fulfilling lives, thereby lessening the burden on their loved ones. The LHON Society is familiar with these reports, having encountered them numerous times. The impact on carers is substantial; Relatives of affected patients shouldered the psychological burden of LHON in our study. Mothers of LHON patients expressed their sense of guilt at having transmitted the condition, despite there being no question of moral culpability. This was evident in discussions regarding expectations of future therapies, where mitochondrial donation and mitochondrial replacement therapy were mentioned by mothers, as a method of preventing transmission of the mutation. Parental guilt and blame, particularly for mothers, has been widely reported for a number of inherited conditions (Chen, 2022) (Carelli, 2017). A mother of a person living with LHON describes the impact on carers **“Firstly your child has suddenly lost their sight, this is devastating, this changes your whole world. You grieve for the life they might not**

	have, you assume that things will be so different going forward. Then the doctors don't know what caused this, you hear many theories, some that stop you in your tracks, will your child live or die. Then you get told that you caused this, you passed on the genetic defect. Your world, your state of mind, it all changes." She went on to discuss living with LHON, **"You become a carer, not just a parent, one parent inevitably can't work full time anymore. You need to be a taxi to school, to hospital appointments. You become a disability advocate, you need to ensure your child's life can continue and that they can achieve anything they wish. Life becomes about ability. You desperately try to self-fund drug treatment because the NHS in England doesn't. You consider moving house to Wales or Scotland to access care. You do anything you can to help your child."** She further explored the impact on quality of life**, "As a parent your quality of life is affected, you stop doing things that you used to do, you are a full-time carer, you make adaptations to the household, the whole family changes things they do to make sure your child can interact. Your mental and physical well-being are affected."** In summary, LHON is a devastating condition that has huge impact on those living with the condition and their carers.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Due to the rare nature of LHON we recognise that our patients are immediately disadvantaged. One patient we spoke to describe the abstract fear of losing sight and being told it could be a brain tumour, multiple sclerosis or hysteria and then being told that the appointment time was over so they would have to leave the clinic. Others describe how it can take more than a year to diagnose with genetic panel testing taking 6 to 12 months before confirmation of LHON. Naturally this is highly destabilising in a person's life, living with fear about their condition at a highly vulnerable time in their lives. Carers describe accessing help and navigating the non-specialist care as incredibly scary, for many this is the first time caring for people with sight loss. When asked to describe the journey from sight loss to diagnosis members gave these thoughts: **"I was working as an apprentice when I started to lose my sight, I lost my job, I was scared and confused. It took 12 months for me to get referred to a specialist and for me to finally have a diagnosis"** and another commented **"I was 16 years old and the week before Easter holidays I noticed I was struggling to read the board at school, we went on holiday during Easter, and I couldn't read menus in restaurants. I told my parents I was struggling and went to an optician who referred me to a GP. We went to our local eye casualty; the doctors didn't seem interested. I was told it's likely to be a brain tumour, Multiple Sclerosis or Hysteria due to my impending GCSE exams. We went back to the hospital several times, one doctor said he didn't know what it was but we would need to leave as he had some laser surgery to do. My parents set out on a mission to solve the puzzle and found a familial link to LHON. We managed to get to the best doctors in the UK and access treatment. It took at least 9 months for a genetic test result. I don't think care is very good until you meet a specialist".** A parent commented **"Finding out you have a genetic disease that you have passed on is horrifying, but still not as bad as the months of fighting for care, trying to find answers. Unfortunately, not having access to the only drug available that can help is the reality you face once you have won the battle for diagnosis."** Without treatment, care is limited to check-ups on sight and little else, as a charity we find that many people drop out of follow up care.
8. Is there an unmet need for patients with this condition?	There is a huge unmet need for people living with LHON. No other treatment is available for people living with LHON. In England, people living with LHON have no access to treatment. This lack of access can lead to some people self-funding, at considerable cost the importation of Idebenone Q10 supplements from the US in the vague hope of achieving the benefits of a licensed pharmaceutical. This is highly concerning and unpredictable, with unknown quality or quantity of the drug being administered.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Very few people have been lucky enough to access the licensed product, Idebenone, however those who have report the following. **"Our child has had full return of sight, we have another child currently on the drug and his sight is improving all the time",** a patient has commented **"My vision was at counting fingers, but I have now had a sight test recorded that shows me as back on charted vision, it's the very worst numbers, but I can actively do things, use my phone, my iPad and can walk to school on my own which allows me to live my life. Idebenone is giving me the ability to be independent".** Another commented **"My daughter's sight has been saved because we got Idebenone early. Time is of the essence Also get referred to Moorfield Hospital as the optic nerve will only get worse"**

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	A number of members have commented that they have tried Idebenone, normally purchased online from US suppliers as a food supplement and not as a licensed pharmaceutical, and that results haven't been as good as hoped. This experience may be due to the nature of a food supplement versus a licensed pharmaceutical.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	We believe that all people living with LHON should have access to Idebenone if a clinician and the patient feel that treatment is appropriate.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There are clear equity issues with residents of Scotland and Wales being able to access the only active treatment, that may enable restoration of sight or improvement of vision, whilst a person diagnosed with LHON in England currently has no chance of sight restoration or improvement. In simple terms, a resident of Galashiels has the hope of improvement of their vision whereas a resident of Newcastle does not, likewise the difference between living in Newport or Bristol may be the difference in chances of leading an independent, fulfilling life.

Other issues

13. Are there any other issues that you would like the committee to consider?	It is very important that the committee carefully consider the implications of functional vision and the benefit to the person living with LHON. For example, the classification of a person's ability to see can be recorded as "off chart", however, the relative functional ability of that person is not captured when discussed as "off chart". For example, in the off-chart category, you may be counting fingers, seeing hand movement or unable to see anything. The difference could be better demonstrated by considering the activities some people can achieve; for example, using a smartphone, or laptop or utilising medical devices that allow you to interact in a sighted world. As such we urge the committee to fully consider the implications of improvement of vision and recommend that they consider functional vision as well as traditional visual acuity. Functional vision has a greater impact on a person's life, quality of life, and ability to live that life. We believe that visual acuity measures do not fully take into account the nuances of changes that have a huge impact on peoples lives.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• LHON is a devasting condition, which has a huge impact on those living with the condition and their carers • The journey to diagnosis is harrowing, and often drawn out • There is no treatment available for those living with LHON in England, there is inequality of care and hence life chances compared to those living in other parts of the United Kingdom • Patients and carers believe that Idebenone does have advantages and report successful treatment outcomes. • Visual acuity scores do not consider visual function, especially when considering off-chart measurement where there is significant variation in functional ability

Bibliography

Carelli. (2017). International Consensus Statement on the Clinical and Therapeutic Management of Leber Hereditary Optic Neuropathy. *Journal of Neuro-Ophthalmology*, 37(4):p 371-381, December 2017. | DOI: 10.1097/WNO.0000000000000570.

Chen. (2022). The Impact of Leber Hereditary Optic Neuropathy on the Quality of Life of Patients and Their Relatives: A Qualitative Study. *Journal of Neuro-Ophthalmolog*, 42(3):p 316-322, September 2022. | DOI: 10.1097/WNO.0000000000001564.

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Single Technology Appraisal

Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

1. Your name	[redacted]
2. Name of organisation	Royal College of Ophthalmologists (RCOphth)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? No A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Ophthalmologists represents the ophthalmic profession in the United Kingdom and supports overseas members in developing countries, building a global community to influence eye health policy and to share standards, training, professional learning and development. We are committed to developing and promoting the highest standards of patient care in ophthalmology and work with organisations in the eye health sector and the healthcare system to influence policy development in the UK. For our international members, we provide e-learning, training and support for developing countries. The governance of the College as a charity and its finances are managed by the Trustee Board
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	I have been involved in clinical trials and/or serve as a consultant for the following companies: Santhera Pharmaceuticals Chiesi GenSight Biologics Neurophth Stoke Therapeutics

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Leber hereditary optic neuropathy (LHON) is a devastating cause of blindness in children and young adults. LHON is a primary mitochondrial genetic disorder with an estimated prevalence of 1 in 30,000 in the United Kingdom. About 90% of cases are due to one of three mitochondrial DNA (mtDNA) point mutations, namely, m.3460G>A in the *MT-ND1* gene, m.11778G>A in the *MT-ND4* gene, and m.14484T>C in the *MT-ND6* gene. Patients develop bilateral severe visual loss due to the selective loss of retinal ganglion cells and subsequent optic nerve degeneration. The visual prognosis is poor with most patients remaining within the legal criteria for blindness (severely sight impaired). Idebenone (Raxone) was approved by the European Medicines Agency (EMA) in 2015 for the treatment of LHON. There is now a substantial body of evidence confirming the visual benefit of idebenone in patients with visual loss from LHON (RHODOS, RHODOS-OFU, Expanded Access Programme (EPA) and LEROS). About 50% of patients treated within five years of disease onset will experience a clinically relevant benefit (either recovery of vision or preventing vision from getting worse) when treated with idebenone 300mgs three times per day. For a disease like LHON, this can have a major impact on quality of life.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Clinically relevant recovery (CRR) has been defined as improvement from an off-chart visual acuity (VA) to reading at least 5 letters on-chart (≤1.6 logMAR), or improvement of at least 10 additional letters (-0.2 logMAR) for those already on-chart. Clinically relevant stabilisation (CRS) has been defined as maintenance of VA < 1.0 logMAR (i.e. VA remains better than 6/60 – the top letter on the standard Snellen chart). Both CRR and CRS are valid metrics for LHON.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	LHON causes severe visual loss and any treatment that can improve the visual prognosis should be made available to patients affected with this mitochondrial genetic disorder.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Patients with LHON in England do not have access to idebenone (Raxone), unlike patients in the rest of the United Kingdom, creating disparity. Idebenone is the only approved treatment for LHON that has been shown to be beneficial.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	The recommended dose for idebenone is 300mgs three times per day (EMA). There is a LHON consensus statement published in 2017, which is still valid, although some items need to be revised based on the latest results from the LEROS study. Carelli V, Carbonelli M, de Coo, I.F, *et al*. (2017). International consensus statement on the clinical and therapeutic management of Leber hereditary optic neuropathy. J Neuro-ophthalmol 37, 371–381.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	LHON is a relatively rare genetic disease. The estimated prevalence is 1 in 30,000 in the UK. There are ~ 20 new cases of LHON per year in the UK. Patients with bilateral visual loss thought to be due to optic nerve involvement are usually referred to a neuro-ophthalmologist for further investigation and treatment (if relevant). Request for LHON genetic testing is available on the NHS although it can take up to three months for the results to become available. As a result, there are frequently delays in reaching a confirmed molecular genetic diagnosis of LHON.
9c. What impact would the technology have on the current pathway of care?	It is likely that treatment with idebenone (Raxone) will be initiated by clinicians with a specialist interest in LHON in a tertiary care setting. Follow-up appointments will be every three to six months with measurement of visual acuity, visual field perimetry and optical coherence tomography imaging. This is standard practice for patients with LHON. No additional resources should be required as the proposed treatment is safe and well tolerated. Based on the findings from the LEROS study, treatment with idebenone (Raxone) should be continued for at least 24 months before deciding that a patient is not a responder. When idebenone (Raxone) is stopped, there is no need for any special monitoring.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Please refer to (9) above
10a. How does healthcare resource use differ between the technology and current care?	Please refer to (9) above
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Please refer to (9) above
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Please refer to (9) above
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	There is a substantial body of evidence supporting the use of idebenone (Raxone) in LHON. Following the EMA marketing authorisation in 2015, this treatment has been approved by national regulatory agencies for the treatment of LHON in several European countries, for example, Germany, Italy and France. Idebenone (Raxone) has been approved for use by the Scottish Medicines Consortium and the All Wales Medicines Strategy Group.
11a. Do you expect the technology to increase length of life more than current care?	LHON is not associated with a reduced life expectancy.
11b. Do you expect the technology to increase	The visual benefit from idebenone is expected to have a significant positive impact on quality of life.

health-related quality of life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Idebenone (Raxone) should be made available to patients with LHON who have experienced visual loss for up to 5 years. There is also evidence from published case series that idebenone (Raxone) could be effective for patients with more chronic disease of up to 10 years.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No additional resources are needed to provide this treatment to patients affected with LHON.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Idebenone (Raxone) should be made available to patients with LHON who have experienced visual loss for up to 5 years.

	Treatment with idebenone (Raxone) can be stopped after two years if there has not been any response.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	There are no disease specific patient reported outcome measures (PROMs) for LHON. An improvement or stabilisation of vision will have a major impact on a patient's quality of life as reported previously in several published studies.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes
17. How do any side effects or adverse effects of the technology affect the management of the	Idebenone (Raxone) is safe and well tolerated.

condition and the patient's quality of life?	

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The studies looking at idebenone (Raxone) have measured visual acuity using either the Snellen or ETDRS charts. Please refer to (7) above.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Visual fields can also be used to assess for treatment benefit in addition to visual acuity although they are not always possible or reliable in patients with relatively poor vision.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	

20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	Not relevant
21. How do data on real-world experience compare with the trial data?	The Expanded Access Programme (EAP) has looked at the benefit of LHON in a real-world setting. Catarino CB, Livonius B. von, Priglinger C, et al. (2020). Real-world clinical experience with idebenone in the treatment of Leber hereditary optic neuropathy. J Neuroophthalmol 40, 558–565.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Patients with LHON in England do not have access to idebenone (Raxone), unlike patients in the rest of the United Kingdom, creating disparity.
22b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions

23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• LHON is a devastating cause of blindness in children and young adults. • Idebenone (Raxone) is the only approved treatment for LHON (EMA 2015). • Treatment with idebenone results in a clinically relevant benefit in ~ 50% of patients. • Idebenone is safe and well tolerated. • Patients with LHON in England do not have access to idebenone (Raxone), unlike patients in the rest of the United Kingdom, creating disparity.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547]

NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NHS England
3. Job title or position	[redacted]

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England has responsibility for commissioning 150 specialised services on a national basis.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There is a clinical commissioning policy in place for treating this condition with Idebenone (Idebenone-for-treating-people-over-12-years-of-age-with-LHO-Neuropathy.pdf (england.nhs.uk) , reference 200401P which concludes that there is not enough evidence to make treatment available
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Current pathway includes regular neuro-ophthalmology outpatient appointments, referral to low-vision services, lifestyle advice and/or genetic counselling.
8. What impact would the technology have on the current pathway of care?	Would potentially offer a treatment option as well as best supportive care.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	There is currently a not routinely commissioned policy in place, so it is not being used in the NHS in England: Idebenone-for-treating-people-over-12-years-of-age-with-LHO-Neuropathy.pdf (england.nhs.uk)
10. Will the technology be used (or is it already used) in the same way	No patient pathways would need to be put in place to establish eligibility and advise on how the product should be taken. Lifestyle advice is also required on avoidance of smoking and limiting alcohol.

as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	Providers would need to offer outpatient appointments to assess eligibility, advise on how the product should be used and offer lifestyle advice.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Outpatients in specialist ophthalmology clinics.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	The treatment is not currently routinely commissioned so any starting and stopping criteria would be developed in line with the NICE decision.
11. What is the outcome of any evaluations or audits of the use of the technology?	There are currently no evaluations or audits.

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	50% of affected males lose vision in their lifetime; 15% of females lose vision. Careful genetic counselling is required.
12b. Consider whether these issues are different from issues with current care and why.	No – not different.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with Leber's hereditary optic neuropathy or caring for a patient with Leber's hereditary optic neuropathy. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

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Patient expert statement

Part 1: Living with this condition or caring for a patient with Leber's hereditary optic neuropathy (LHON)

Table 1 About you, LHON, current treatments and equality

1. Your name	James Ferguson
2. Are you (please tick all that apply)	☒ A patient with LHON? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with LHON? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	LHON Society
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

Patient expert statement

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with LHON? **If you are a carer (for someone with LHON?) please share your experience of caring for them**	I was diagnosed with LHON in 2006 and through my work for the LHON Society have met many more people with LHON over the past decade. LHON is a devastating condition that caused irreversible central vision loss. It happened to me when I was 23 and at the time it felt like my life was over. The condition most commonly impacts young men but can affect anyone with the gene at any stage in life. To understand the experience of LHON you need to imagine what it would be like to no longer see anything in detail. No longer be able to see faces or read text. Every aspect of your life becomes far more difficult and challenging. Mobility; I cannot drive and so I am reliant on public transport or taxis. I have a disabled persons railcard to save a 1/3 on my journeys and can get assistance when using trains or airports. Public transport is not always an option which means spending more money on taxis to get to places or visit people. Self-Care; I cannot see my face to shave or my nails to cut. My partner trims my beard otherwise I make a mess. I cut my nails through feel. I can't tell if a shirt is ironed and need my partner to confirm if I am dressed appropriately. Activities of daily life; Every aspect of my life is much harder. If I go shopping I ask for assistance so I can find the food items I want. I used to love playing and watching football but these are no longer an option. I do sit with my face an inch from the screen to watch matches but in the past I went to the games live. This was a huge part of my life which is no longer possible. I do work and have a career as a psychological therapist in the NHS.. However, the unemployment rates are high for blind people. Assistive technology is very

	expensive to buy. The software for my computer costs £1000. Access to Work do provide grants but only once you have employment. This can be a barrier for people who want to gain experience through volunteering but can't afford the software. Relationships; I do have a long term partner but I had many years as a single man. It is difficult to meet people when you can't see faces and may struggle to find certain places. There is stigma around blindness and this impacts people's perception of you. Cooking can be challenging. I have purchased equipment for my kitchen that will talk to me. For example scales and thermometer . I use magnifying glasses to try and read packets and feel my way. I will often need my partner to clarify what I am looking at. Socialising is difficult and can cause a lot of anxiety. I try to recognise people from their voices but will need them to tell me who they are. The impact on mental health can be huge. The reality is for most people it impacts them in their late teens and early twenties. When you are trying to build your life, find a career, a relationship, try new experiences. At a stage in life when you are building independence you become more dependent on others. This impacts your sense of self. This is all taken away. It is very common for people to go through periods of depression and anxiety. I recall an incredible sense of hopelessness when I was first diagnosed, unable to imagine any sort of life for myself. Many people access therapy to help them cope with this difficult time. People often feel very vulnerable and alone as they try to adjust to life with limited sight. There can be many embarrassing moments in daily life. For example here are some of mine; walking into the womens toilets, realising you are on the wrong train/ bus, talking to a cardboard cut out that I thought was a person.

	I hope the above gives some sense of how this disease impacts every aspect of your life. There are costs at every level to buy new assistive technology, bigger TVS, pay for taxis. There is often a long period of lost earnings and your career progression is hindered. It takes time for people to adjust to all the challenges of limited vision, the related depression and anxiety and rebuild confidence. Idebenone is a safe drug that gives people the chance to regain some of their sight which would greatly improve their quality of life. It can improve sight to a level where people are less dependent on others and thus are more likely to build a career and find a relationship.
7a. What do you think of the current treatments and care available for LHON on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**7a. Not good enough. The message is; this condition is uncurable, you are now discharged.** **7b. These views are consistent across the LHON community in England.**
8. If there are disadvantages for patients of current NHS treatments for LHON (for example, how they are given or taken, side effects of treatment, and any others) please describe these	There currently are no treatments available on the NHS in England.
9a. If there are advantages of idebenone over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	**There are no other treatments.** **The advantage of Idebenone is that , to my knowledge, there are no side effects. It will not work for everyone but can have a positive impact for those it does. It can help people to regain independence with activities of daily life such as cooking, shopping, travel and socialising. Increased levels of vision can have a huge impact on an individual's confidence and general mental health. Employment becomes easier as more jobs become an option.**

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does idebenone help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**9b. The impact on mental health. Increased vision will undoubtedly reduce levels of anxiety and depression. This makes it easier to engage in all aspects of life. You will be less dependent on others, more likely to build a fulfilling career and less likely to need any financial support from the government such as disability living allowance.**
10. If there are disadvantages of idebenone over current treatments on the NHS please describe these. For example, are there any risks with idebenone ? If you are concerned about any potential side effects you have heard about, please describe them and explain why	There are no other treatments available. There are no side effects to Idebenone.
11. Are there any groups of patients who might benefit more from idebenone or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	To my knowledge there are no preferential groups.
12. Are there any potential equality issues that should be taken into account when considering LHON and idebenone? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil	If you live in England you are disadvantaged as you cannot get access to this drug unless you are prepared to buy it yourself over the internet. As I said above the average age of onset is late teens and early twenties. Not offering this drug is leaving those diagnosed with LHON hugely disadvantaged compared to their peers. They are not able to drive, can struggle to find meaningful employment, can be more dependent on others will have many missed opportunities at a key stage in their life. They are disadvantaged as every aspect of their life becomes harder or impossible. To find ways round most tasks can cost more money to buy the assistive

partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	technology, pay for the taxi or find someone to help. You have to work infinitely harder just to get to the same plac.e
13. Are there any other issues that you would like the committee to consider?	LHON is a devastating condition that leaves people with sight loss for the rest of their life. Idebenone gives people a chance to recover some of that vision.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with Leber's hereditary optic neuropathy or caring for a patient with Leber's hereditary optic neuropathy. The text boxes will expand as you type.

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Patient expert statement

Part 1: Living with this condition or caring for a patient with Leber's hereditary optic neuropathy (LHON)

Table 1 About you, LHON, current treatments and equality

1. Your name	Lily Mumford
2. Are you (please tick all that apply)	☒ A patient with LHON? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with LHON? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	LHON Society
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

Patient expert statement

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with LHON? **If you are a carer (for someone with LHON?) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for LHON on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for LHON (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of idebenone over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does idebenone help to overcome or address any of the listed disadvantages of current treatment that**	

you have described in question 8? If so, please describe these	
10. If there are disadvantages of idebenone over current treatments on the NHS please describe these. For example, are there any risks with idebenone ? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from idebenone or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering LHON and idebenone? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547]

Clinical expert statement

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Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

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NICE National Institute for Health and Care Excellence

Part 1: Treating Leber's hereditary optic neuropathy (LHON) and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	MARCELA VOTRUBA
2. Name of organisation	CARDIFF & VALE UNIVERSITY HEALTH BOARD/ CARDIFF UNIVERSITY
3. Job title or position	PROFESSOR OF OPHTHALMOLOGY
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with LHON? ☒ A specialist in the clinical evidence base for LHON for technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NONE with tobacco industry. I have been involved in clinical trials and/or serve as a consultant for: Santhera Pharmaceuticals Chiesi GenSight Biologics

	Stoke Therapeutics
8. What is the main aim of treatment for **LHON** (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim of this proposed treatment is to reduce the eventual level of vision loss. There may be a stop to progression or stabilisation of vision. Recovery of vision has also been documented. Mobility will be increased if visual acuity is retained and hence disability will be reduced.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	This has been defined in published papers and reviews. Clinically relevant recovery (CRR) has been defined as improvement from an off-chart visual acuity (VA) to reading at least 5 letters on-chart (≤1.6 logMAR), or improvement of at least 10 additional letters (-0.2 logMAR) for those already on-chart. Clinically relevant stabilisation (CRS) has been defined as maintenance of VA < 1.0 logMAR (i.e. VA remains better than 6/60 – the top letter on the standard Snellen chart).
10. In your view, is there an unmet need for patients and healthcare professionals in LHON?	Without any doubt at all there is an unmet need for patients and clinicians alike. LHON causes profound loss of vision and there is currently no treatment.
11. How is LHON currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	There is currently no treatment for LHON in the NHS England. Care is supportive. There are no written formal clinical guidelines adopted in the absence of Raxone.

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The pathway of care currently is that a patient is referred via an optometrist, GP, or neurology/ other medical team, to an ophthalmology specialist- neuro-ophthalmology or gene tic eye disease clinic. Clinical assessment is consistent. Genetic testing is now widely available and caried out in the specialist clinic. It takes 6-12 weeks on average- too long! The patient is seen more at the outset: i.e., - at referral for 1st visit- clinical diagnosis (Visual Acuity, imaging with OCT, visual field/ perimetry, gene test taken - then for results of genetic testing & registration as significantly visually impaired, - then follow-up at 6 months, - then 6 monthly or eventually annually. The patient pathway is relatively well defined with some local variation. The technology would have little if any impact on these assessments and reviews. My experience is from NHS Wales. Idebenone is recommended at 300mg three times per day, as per the EMA. A LHON consensus statement from 2017, outlines the best practice from trials- albeit this statement now needs to be updated in the light of more recent papers- however, much of the recommendations are still valid.

	Indeed, recent data would suggest a potential for treatment of patients longer after the onset of loss of vision (e.g., start treatment up to 5 years from vision loss). Recent published evidence (LEROS study) supports use for at least 24 months if there is evidence of a response. Carelli V, Carbonelli M, de Coo, I.F, *et al*. (2017). International consensus statement on the clinical and therapeutic management of Leber hereditary optic neuropathy. J Neuro-ophthalmol 37, 371–381. The technology would introduce a treatment into the pathway of care and provide hope to patients currently without any active intervention in England.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Current care has no therapeutic options. The additional resources will be the drug itself and a shift from annual follow-up appointments to 6 monthly appointments for approx. 2 years. The setting needs to be tertiary specialist care in ophthalmology. Very little investment is needed- the specialists are there, the equipment needed is there.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care?	Yes there are likely to be clinically meaningful benefits for some patients.

• Do you expect the technology to increase health-related quality of life more than current care?	LHON does not explicitly affect length of life. The treatment will not have any notable impact on this. Health-related quality of life is likely to be improved and has been documented in some studies.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	no
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Since current care is no treatment this is a change. Please see patient pathway above. It will not be difficult. No additional resources would be needed.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients will be assessed by a tertiary expert clinic- often neuro-ophthalmology, ophthalmic genetics, and started on therapy after the clinical diagnosis is confirmed. A genetic test is already carried out. Follow-up appointments will be every three to six months with measurement of visual acuity, visual field perimetry and optical coherence tomography imaging. This is standard practice for patients with LHON. No additional resources should be required as the proposed treatment is safe and well tolerated.

	Based on the findings from the LEROS study, treatment with idebenone should be continued for at least 24 months before deciding that a patient is not a responder. No additional testing is needed.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The instruments used for quality of life in vision impairment are being re-evaluated with focus on PROMS and some degree of re-thinking to make them more relevant. Even with this caveat there is evidence of improved quality of life.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	I do consider it to be innovative and there is potential to make a difference in health and quality of life. The technology is not ground-breaking and the benefits are not a complete reversal of vision loss or major restoration of sight to normal- but there are clearly documented benefits in many patients. It is a step-change. There is no alternative viable therapy imminent and other therapies like gene therapy may still take time. The use of this technology does address a particular and definite unmet need in the patient population.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Very few if any significant side effects are reported. Even minor side effects are rare.

20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	• Yes they do reflect UK clinical practice. Most clinics are now using LogMAR vision especially for patients with so called low or reduced vision- and the charts are easily used and widely available. Clinics can and do easily measure visual field and colour vison. There would not need to be any major changes in NHS clinics to monitor the therapy. • What, in your view, are the most important outcomes, and were they measured in the trials? Visual acuity is the most important outcome and this was measured. Visual field is also very important to patients- there is evidence in follow-on studies that this also improves. • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? NA • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? I do not know of any. •
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
22. How do data on real-world experience compare with the trial data?	Real-world evidence in an expanded access program compare favourably with trial data. The data was published; Catarino CB, Livonius B. von, Priglinger C, et al. (2020). Real-world clinical experience with idebenone in the treatment of Leber hereditary optic neuropathy. J Neuroophthalmol 40, 558–565.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any	There clearly exists inequality at the present time- patients in England do not have approved access to this treatment.

potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	I do not anticipate any exclusion of patients on the basis of the factors listed.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

LHON is a devastating cause of blindness in males, females and can affect all ages, from children to mature adults.

No current treatment other than idebeneone (Raxone) has been approved.

Idebenone can result in clinically relevant improvement in vision.

Idebenone is safe and has very few side effects.

My patients in Wales can access idebenone but there is a UK wide disparity in access.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **22 March 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating Leber's hereditary optic neuropathy (LHON) and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Patrick Yu Wai Man
2. Name of organisation	University of Cambridge and Moorfields Eye Hospital
3. Job title or position	Professor of Ophthalmology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with LHON? ☒ A specialist in the clinical evidence base for LHON for technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I have been involved in clinical trials and/or serve as a consultant for the following companies: Santhera Pharmaceuticals Chiesi GenSight Biologics Neurophth

	Stoke Therapeutics
8. What is the main aim of treatment for **LHON** (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	I wrote the submission for the Royal College of Ophthalmologists. I have provided additional information in this document as part of my personal statement as a neuro-ophthalmologist who sees a significant number of patients with LHON in my clinical practice (Addenbrooke's Hospital in Cambridge and Moorfields Eye Hospital in London).
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Patients with LHON will frequently report a subjective improvement in vision before this can be documented formally (visual acuity and/or visual fields). Clinically relevant recovery (CRR) has been defined as improvement from an off-chart visual acuity (VA) to reading at least 5 letters on-chart (≤1.6 logMAR), or improvement of at least 10 additional letters (-0.2 logMAR) for those already on-chart. Clinically relevant stabilisation (CRS) has been defined as maintenance of VA < 1.0 logMAR (i.e. VA remains better than 6/60 – the top letter on the standard Snellen chart). Both CRR and CRS are valid metrics for LHON. Improvement in visual fields is characterised by gaps (fenestrations) forming in the central scotoma (fenestrations) that in some cases expand and coalesce together.
10. In your view, is there an unmet need for patients and healthcare professionals in LHON?	LHON is a devastating blinding disease that affects otherwise young and healthy individuals. The only approved treatment for LHON (Idebenone, Raxone) is not currently available on the NHS in England.
11. How is LHON currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	Treatment for LHON in England remains supportive.

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	There is now a strong body of evidence about the benefit of using Idebenone in patients with LHON treated within five years of disease onset. The LEROS study was published in Cell Reports Medicine on the 19th of March 2024. https://www.cell.com/cell-reports-medicine/pdfExtended/S2666-3791(24)00060-0
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I would treat patients with LHON with disease duration of up to five years.

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Most patients with LHON are seen in specialist clinics in tertiary centres. I do not foresee any difficulties in delivering treatment with Idebenone.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Based on the LEROS study and the Expanded Access Programme (EAP), I would treat for two years and then stop if there has not been any visual benefit. Catarino CB, Livonius B. von, Priglinger C, et al. (2020). Real-world clinical experience with idebenone in the treatment of Leber hereditary optic neuropathy. J Neuroophthalmol 40, 558–565. I would continue treatment for as long as the patient is reporting a benefit. Once the improvement has plateaued, the consensus statement from a group of LHON experts was that treatment should be continued for one year and then stopped. Carelli V, Carbonelli M, de Coo, I.F, et al. (2017). International consensus statement on the clinical and therapeutic management of Leber hereditary optic neuropathy. J Neuro-ophthalmol 37, 371–381.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some	Yes – to some extent. There is no dedicated set of patient-reported outcome measures (PROMs) that fully captures the lived experience of patients affected with LHON. Chen BS, Galus T, Archer S, Tadić V, Horton M, Pesudovs K, Braithwaite T, Yu-Wai-Man P (2022). Capturing the experiences of patients with inherited optic

been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	neuropathies: a systematic review of patient-reported outcome measures (PROMs) and qualitative studies. Graefes Arch Clin Exp Ophthalmol 260(6),2045–2055.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Providing Idebenone to patients affected with LHON in England will give ~50% of them the opportunity to achieve a better visual outcome.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Idebenone has a very good safety profile even with long-term use.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The RHODOS, EAP and LEROS studies provide us a with a clear set of data about which group of patients should be treated with Idebenone at a daily dose of 300mgs three times per day. - Treat patients with duration of visual loss of up to five years - Stop the treatment after two years of treatment if no response
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	

22. How do data on real-world experience compare with the trial data?	The LEROS and EAP results are consistent.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	Idebenone (Raxone) has been approved for use by the Scottish Medicines Consortium and the All Wales Medicines Strategy Group.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1. LHON is a devastating cause of blindness in children and young adults.
2. Idebenone (Raxone) is the only approved treatment for LHON (EMA 2015).
3. Treatment with idebenone results in a clinically relevant benefit in ~ 50% of patients.
4. Idebenone is safe and well tolerated.
5. Patients with LHON in England do not have access to idebenone (Raxone), unlike patients in the rest of the United Kingdom, creating disparity.

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BMJ TAG

Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547]

STA Report

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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Melina Vasileiou	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Benjamin Farrar	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Archie Walters	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Kate Ennis	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the EAG report.

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List of Abbreviations

AE	Adverse events
ARMD	Age-related macular degeneration
BCVA	Best-corrected visual acuity
CaRS	Case Record Survey
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CF	Count fingers
CGIC	Clinical Global Impression of Change
CRB	Clinically relevant benefit
CRR	Clinically relevant recovery
CRS	Clinically relevant stabilisation
CS	Company Submission
CSR	Clinical Study Report
EAG	External Assessment Group
EAP	Expanded Access Program
EBMR	Evidence-based Medicine Reviews
EP	Efficacy population
ETDRS	Early Treatment Diabetic Retinopathy Study
EUCTR	EU Clinical Trials Register
HRQoL	Health related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IQR	Interquartile range
ITT	Intent-to-treat
KOL	Key opinion leader
LHON	Leber's hereditary optic neuropathy
LOCF	Last observation carried forward
logMAR	Logarithm of the minimum angle of resolution
LP	Light perception
LS	Least squares
LY	Life years
MA	Marketing authorisation
mITT	Modified intent-to-treat
MMRM	Mixed-Model for Repeated Measures
NH	Natural history
NICE	National Institute for Health and Care Excellence
NR	Not reported

OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PSA	Probability sensitivity analysis
PSM	Propensity-score matching
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life years
QoL	Quality of life
RCT	Randomised controlled trial
RGC	Retinal ganglion cells
ROBINS-I	Risk of Bias In Non-Randomised Studies-of Interventions
ROI	Republic of Ireland
RWE	Real-world evidence
SAE	Serious adverse events
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
STA	Single Technology Appraisal
TTO	Time-trade off
VA	Visual acuity
VAS	Visual Analog Scale
VF	Visual function
WHO ITCRP	World Health Organisation International Clinical Trials Registry Platform
WTP	Willingness-to-pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.4 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	There is no precise effectiveness estimate for treatment with idebenone beyond six months to draw robust conclusions about its long-term clinical and cost-effectiveness.	3.2.4, 3.4
2	The benefit of treatment with idebenone may be larger in subgroups of patients but the limited sample sizes available in the current evidence leads to a high degree of uncertainty.	2.3.5, 3.3.4
3	The company model structure is inappropriate given the insufficient evidence to support the high number of health states in the economic model. Additionally, there are limited data to provide robust transition probabilities for the company's model and, given the modest differences in HRQoL between the health states, the justification for a high number of health states is weak.	4.2.2
4	The model fails to accurately replicate the SoC treatment effects as measured in studies and clinical trials, with the company failing to derive a treatment effect using all appropriate available data.	4.2.4
5	The model lacks the functionality to allow idebenone and SoC transition probabilities to vary according to treatment effectiveness uncertainty. The PSA therefore fails to account for treatment effectiveness uncertainty.	4.2.4

Abbreviations: EAG, External Assessment Group; HRQoL, Health related quality of life; PSA, probabilistic sensitivity analysis, SoC, Standard of care

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Improving logMAR recovery;

Overall, the technology is modelled to affect costs by:

- Being more costly than the current standard of care (SoC);
- Reducing the requirement for additional health care resources;

The modelling assumptions that have the greatest effect on the ICER are:

- The SoC treatment effect;
- Off chart blindness health related quality of life utilities.

1.3 Summary of the EAG's key issues

Table 2. Issue 1: Lack of robust long-term treatment effect estimates for idebenone and standard of care

Report section	3.2.4; 3.4
Description of issue and why the EAG has identified it as important	Randomised controlled trial (RCT) evidence on the efficacy of idebenone compared to standard of care (SoC) is available for up to six months, while evidence on the long-term treatment is limited to observational data. The company uses two unmatched populations from the real-world observational Expanded Access program (EAP) and the Case record survey (CaRS) natural history studies to model the long-term treatment effects of idebenone and SoC, respectively, resulting in an estimate at high risk of bias due to imbalances in prognostic factors between patients from the data sources. Although no matched control analyses are provided in the original CS, following a request by the EAG at the clarification stage, the company provided a propensity-score matching (PSM) analysis of changes in patient's best visual acuity between LEROS and CaRS-I and CaRS-II at Month 24. The EAG notes there were limitations to the PSM analysis and the EAG is mostly concerned that only a limited amount of CaRS follow-up data were included in the analyses by choosing to only analyse a single visit pair, rather than all available data, for SoC patients. Matching resulted in a very limited sample and the baseline characteristics suggest issues with the matching persisted. As a result, the EAG considers there to be a lack of a precise estimate for long-term treatment benefit with idebenone. The EAG considers this to be a fundamental issue impacting the technology appraisal, as with no long-term RCT data or an alternative approach involving adequate matching, a robust conclusion on clinical and cost-effectiveness of long-term treatment with idebenone cannot be drawn.
What alternative approach has the EAG suggested?	The EAG considers that matching the idebenone and SoC cohorts would provide a less biased method to model the long-term treatment effect of idebenone and SoC compared to the company's original approach using unmatched populations and requested that the company conduct a matched-controlled analysis using the LEROS trial with a CaRS matched controlled analysis. In regard to the company's PSM analyses provided following the EAG's request at the clarification stage, the EAG considers matching patients between LEROS and CaRS at baseline and then including all available data from subsequent follow-up visits in the analysis would be a preferable approach, instead of using a single baseline and 24-month visit window only.
What is the expected effect on the cost-effectiveness estimates?	The EAG considers that if a more appropriate matching methodology had been used the ICER would likely increase given that in the matched control analysis provided using LEROS and CaRS patients demonstrates no significant difference in treatment effects.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that the PSM analysis presented in the company's response to clarification does not provide strong evidence of a clinically meaningful long-term treatment benefit of idebenone over SoC for the treatment of LHON, but it is the only available long-term matched-control comparison of changes in patients' best logMAR VA over time. Thus, this is considered by the EAG to be the most appropriate analysis of the comparative effectiveness of long-term idebenone treatment compared to SoC that is currently available. However, considering the limited sample/amount of data resulting from the matching, the EAG considers further analyses making use of all available data might help resolve remaining uncertainties regarding long-term effectiveness of treatment with idebenone.

Abbreviations: CaRS, Case-record survey; CS, Company submission; EAG, External Assessment Group; EAP, Expanded Access Program; PSM, Propensity-score matching; RCT, Randomised controlled trial; SoC, Standard of care.

Table 3. Issue 2 Subgroup effects

Report section	2.3.5; 3.3.4
Description of issue and why the EAG has identified it as important	The EAG's clinical experts note that the benefit a patient may receive from idebenone treatment may be larger in subgroups of patients treated prior to nadir (i.e. <1 year since symptom onset), with baseline logMAR <1 or in subgroups of patients with a particular genotype. The EAG notes that the clinical trials were not powered to detect subgroup effects with subgroup sample sizes being too small to support meaningful conclusions about a difference in the magnitude of treatment effect between different subgroups of patients.
What alternative approach has the EAG suggested?	The EAG asked the company to comment on whether they believe the clinical and cost effectiveness of idebenone may be larger in a subgroup of patients treated either early on in the disease course or with a baseline logMAR <1 and to provide relevant scatterplots and regression analyses. The company do not believe that results will differ and consider current evidence from the RHODOS trial, the LEROS trial and the EAP show a benefit in patients regardless of disease stage but did not provide relevant scatterplots or analyses for different subgroups of patients across trials.
What is the expected effect on the cost-effectiveness estimates?	It's anticipated that idebenone may be more cost effective in specific subgroups.
What additional evidence or analyses might help to resolve this key issue?	Future trials including larger datasets, sufficiently powered to detect subgroup effects would be useful to resolve uncertainties regarding treatment effectiveness. However, the EAG recognises that LHON is a rare disease, and this may present a challenge.

Abbreviations: EAG, External Assessment Group; EAP, Expanded Access Program; logMAR, logarithm of the minimum angle of resolution standard of care.

Table 4. Issue 3 Cost effectiveness model structure

Report section	4.2.2
Description of issue and why the EAG has identified it as important	The EAG considers that the company's model is flawed and potentially inappropriate for decision making as there is insufficient evidence to support the high number of health states in the economic model. Additionally, there are limited data to provide robust transition probabilities for the company's model and, given the modest differences in HRQoL between the health states, the justification for a high number of health states is weak.
What alternative approach has the EAG suggested?	The EAG has suggested an alternative model structure, which the company has used in a scenario analysis.
What is the expected effect on the cost-effectiveness estimates?	Using the EAG's preferred model led to an increase in the ICER between idebenone and SoC treatments.
What additional evidence or analyses might help to resolve this key issue?	No additional analysis required

Abbreviations: EAG, External Assessment Group; HRQoL, health related quality of life; ICER, incremental cost effectiveness ratio; SoC, standard of care.

Table 5. Issue 4 Model standard of care treatment effects

Report section	4.2.4
Description of issue and why the EAG has identified it as important	The modelled SoC treatment effects do not replicate the RHODOS, RHODOS-OFU or the matched analysis study findings with mean change in logMAR from baseline being substantially greater in the company base case than in the RHODOS trial at 6 months. The EAG additionally considers that a robust SoC treatment effect, which replicates the trial results, may be derived from the available CaRS -I and -II data. However, limited patient observations are used from these studies to inform the SoC treatment effect.
What alternative approach has the EAG suggested?	The EAG has suggested informing the SoC transition probabilities using the patient observations from the CaRS studies matched to LEROS patient population or alternatively the RHODOS-OFU study as the EAG considers these data sources the most appropriate as described in key issue 1 .
What is the expected effect on the cost-effectiveness estimates?	The EAG expects that aligning the modelled SoC treatment effects to that of either the matched CaRS population or RHODOS-OFU will lead to an increase in the ICER, as can be seen in the illustrative scenario conducted by the EAG.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that if the company validates the modelled SoC treatment effect using appropriate study or trial data this would resolve the issue.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost effectiveness ratio; SoC, standard of care.

Table 6. Issue 5 Failure of the PSA to account for treatment effect uncertainty

Report section	4.2.4
Description of issue and why the EAG has identified it as important	As the model lacks the functionality to allow idebenone and SoC transition probabilities to vary according to treatment effectiveness uncertainty the PSA fails to account for treatment effectiveness uncertainty. As such, the EAG is concerned that the probabilistic results are unfit for decision making given the high degree of uncertainty in the treatment effects that are not captured in the PSA results. Additionally, the EAG considers the company's justification for not including transition probabilities in the PSA, namely that this would lead to additionally uncertainty in the PSA results, is unfounded given that the aim of the PSA is to account for parameter uncertainty.
What alternative approach has the EAG suggested?	The EAG has suggested that transition probabilities be made probabilistic when calculating the PSA results.
What is the expected effect on the cost-effectiveness estimates?	Cost effectiveness estimates will be more robust and reliable by account for the treatment effectiveness uncertainty.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that only allowing transition probabilities to made probabilistic would resolve this issue.

Abbreviations: EAG, External Assessment Group; PSA, probabilistic sensitivity analysis; SoC, standard of care.

1.4 Summary of EAG's preferred assumptions and resulting ICER

Table 7. EAG's preferred model assumptions

Scenario	Incremental costs	Incremental QALYs	ICER (change from company base case
Company base case	[redacted]	[redacted]	18,758
EAG preferred model structure	[redacted]	[redacted]	27,053 (+8,295)
Using the LEROS study data to derive the idebenone long term treatment effect	[redacted]	[redacted]	28,459 (+9,701)
Applying the LEROS idebenone transition probabilities to SoC patients after RHODOS	[redacted]	[redacted]	59,061 (+40,303)
Adjusting the idebenone treatment discontinuation weighted average calculation and increasing the proportion who discontinue treatment to 10.8%	[redacted]	[redacted]	21,022 (+2,264)
Using the utilities calculated from Lawrence *et al.* that include patients from the Republic of Ireland*[2]	[redacted]	[redacted]	27,780 (+9,022)
No carer disutility applied	[redacted]	[redacted]	21,019 (+2,261)
Applying additional healthcare resource costs according to Meads *et al.**[3]	[redacted]	[redacted]	31,631 (+12,873)
Applying supportive living cost as a one-off cost	[redacted]	[redacted]	25,899 (+7,141)
Applying outpatient care cost as a one-off cost	[redacted]	[redacted]	19,595 (+837)

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

*EAG preferred model assumption also required

Table 8. EAG base case results

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	130,269
Probabilistic results*							
SoC	[redacted]	-	[redacted]	-	-	-	-
Idebenone	[redacted]	-	[redacted]	[redacted]	-	[redacted]	126,422

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SoC, standard of care.

*Probabilistic results do not account for idebenone and SoC treatment effectiveness uncertainty

2 Introduction and background

2.1 Introduction

This report contains the External Assessment Group's (EAG's) critique of the clinical and cost effectiveness evidence submitted for the Single Technology Appraisal (STA) of idebenone (brand name: Raxone®; Chiesi Farmaceutici, Parma, Italy) for treating visual impairment in Leber's Hereditary Optic Neuropathy (LHON) in people 12 years and over [ID547].

2.2 Background

Section B.1.3 of the Company Submission (CS) provides an overview of LHON. LHON is a rare mitochondrial genetic disease that most often affects young adult males.[4] LHON causes degeneration of the optic nerve, and people with LHON experience a sudden and rapid loss of central vision, usually within weeks of symptom onset.[5] Approximately 95% of people with LHON have one of three mitochondrial DNA (mtDNA) mutations: m.11778G>A; m.14484T>C; and m.3460G>A.[4] Such mutations lead to the dysfunction of complex I of the electron transport chain, causing oxidative stress and the eventual apoptosis of retinal ganglion cells.[6, 7]

Over 1 in 1,000 individuals in the UK Biobank carry a mutation with the potential to cause LHON,[8] but the prevalence of LHON in the UK is rare, i.e., the disease has low penetrance.[8] The topic selection oversight panel for the current appraisal estimated that 471 patients would be eligible for idebenone treatment in clinical practice in England, should the technology be approved for routine commissioning.[9] This figure was calculated based on prevalence estimates for LHON in England from Yu-Wai-Man *et al.* 2003 of around 1 in 31,000 individuals.[10]

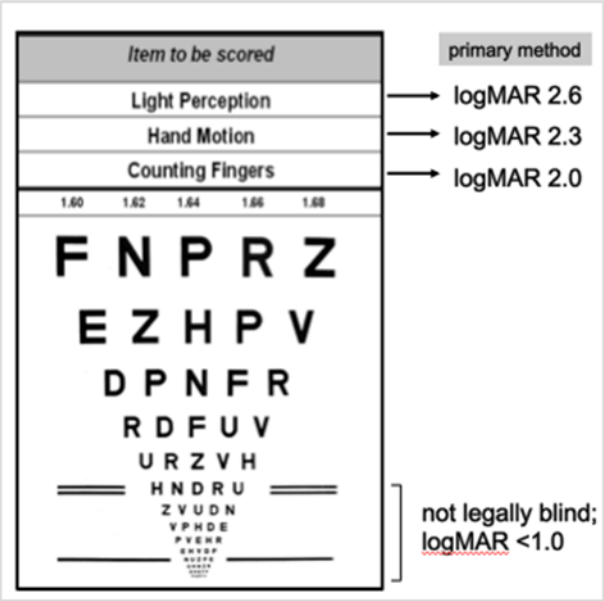
Initially, people with LHON present with a rapid loss of central vision.[5] After presentation, these individuals may be tested and treated for other causes of vision loss before a diagnosis of LHON is suspected and/or confirmed through genetic testing.[5] The typical disease course of LHON can be separated into three phases: subacute/acute, dynamic and chronic. In the acute phase of LHON, central vision is lost in both eyes (25% to 50% of the time) or sequentially (50% to 75% of the time), with the second eye usually being affected to a similar degree as the first eye weeks or months later.[11] The point at which an eye's visual acuity (VA) is lowest is termed nadir, which is usually reached a few months after the onset of symptoms.[12] Following nadir, a patient's VA usually stabilises during a dynamic phase around 6 to 12 months after symptom onset, before the disease enters a chronic phase >12 months after symptom onset.[13] In chronic LHON, a patient's VA is usually stable, but the EAG's clinical experts noted that some further decline is possible.[14] The EAG's clinical

experts also highlighted that the disease course of LHON is heterogeneous, and the natural history of LHON outlined above and in the CS reflects a "textbook" case of LHON. For example, the initial rate of vision loss may be slow and progressive for some patients, and nadir may not be reached until a year or more after initial diagnosis.

2.2.1 Disease progression and disease burden

In clinical trials, vision loss in LHON is usually measured using the Logarithm of the Minimum Angle of Resolution (logMAR) chart of VA (Figure 1).

Figure 1. The logMAR scale including 'off-chart VA' categories (Reproduced from CS Figure 2)



LogMAR values are assessed using the ETDRS charts.
Source: CS Figure 2
Abbreviation: logMAR, Logarithm of the minimum angle of resolution

In the CS, the Company distinguish between the following categories of vision loss based on logMAR values:

- LogMAR <1.0: Not legally blind;
- LogMAR ≥1.0: Legally blind;
- LogMAR ≥1.6: Off-chart.

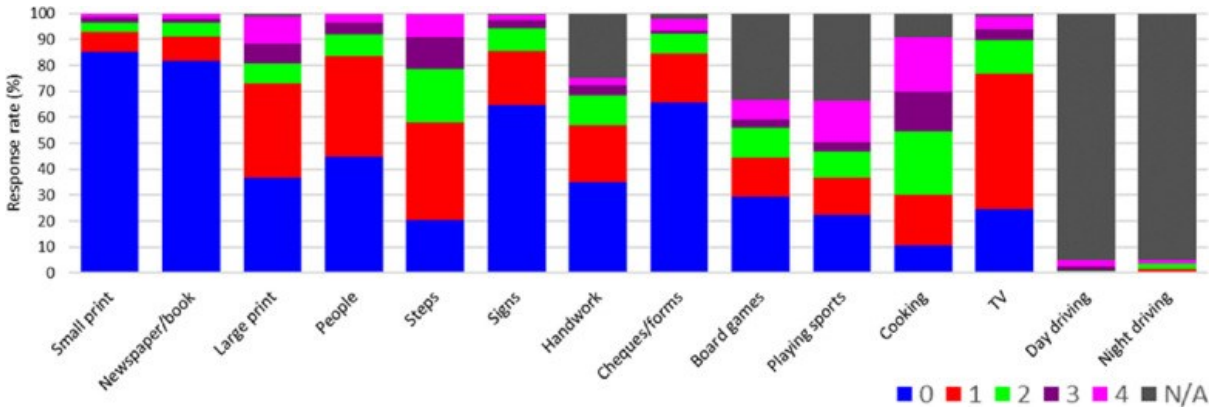
The EAG's clinical experts highlighted that the term "legally blind" is no longer used in clinical practice, and instead people with vision loss may be registered as sight impaired or severely sight impaired. Based on this, the EAG considers the following categories of vision loss based on logMAR values to reflect clinically meaningful categories recognised in English clinical practice:

- LogMAR <0.3: Not sight impaired, able to drive;
- 0.3≤ LogMAR <1.0: Not sight impaired, unable to drive;
- LogMAR ≥1.0: Sight impaired, on-chart sight;
- LogMAR ≥1.6: Sight impaired, off-chart sight.

The EAG notes that the exact criteria for registering an individual as sight impaired or severely sight impaired depends not only on measures of visual acuity, but also on the degree of visual field loss.[15]

LHON affects many dimensions of a person's life. Interview studies of LHON patients and caregivers highlight how LHON can severely impair a person's day to day activities and independence and likelihood of employment.[16, 17] The studies highlight LHON can have a large negative influence on the quality of a person's social, physical and emotional life.[16, 17] Depression, anxiety, and suicidal thoughts are reported for some patients, and people with LHON, and sight loss more broadly, often report stigmatisation following sight loss.[17] The Visual Function Index (VF-14) Questionnaire, originally developed as an index of functional impairment following cataract surgery,[18] is a disease-specific questionnaire designed to assess the level of visual impairment that has been used on a range of ophthalmologic conditions. Questions include: "Do you have any difficulty, even with glasses, reading small print, such as labels on medicine bottles, a telephone book, or food labels?" and "Do you have any difficulty, even with glasses, recognizing people when they are close to you?". Responses are measured on a 5-point scale from "No" to "Unable to do this activity". In a recent VF-14 survey of 196 LHON patients in the UK, Netherlands and Germany, most patients responded either 0 ("Unable to do this activity), 1 ("a great deal of difficulty") or NA to most questions.[1] These data are displayed in Figure 2 to provide an overview of the visual symptom burden of LHON. While the VF-14 can describe some of the symptoms of LHON, the psychometric validity of the VF-14 as a clinical trial endpoint in LHON has been criticised on several measurement grounds including disordered response thresholds and its multidimensionality.[1]

Figure 2. Chen *et al.* distribution of responses to items of the VF-14 by 196 people with LHON. Reproduced from Chen *et al.* Figure 1.[1]



2.2.2 LHON genotypes and spontaneous recovery

Three genotypes, m.11778G>A, m.14484T>C, and m.3460G>A, comprise around 95% of the LHON population.[4] A variety of other LHON genotypes make up the remaining ~5% of the population; however, the EAG's clinical experts highlighted that these mutations are harder to identify as tests for these are not routinely available. Even with complete mtDNA sequencing, interpreting the results of genetic tests for LHON when an individual is negative for one of the three primary mutations is difficult due to the rarity of presentation and characterisation of any suspected disease-causing allele.

LHON genotype is a key prognostic factor for individuals with LHON and affects the likelihood of spontaneous recovery of visual acuity.[10] Spontaneous recovery is inconsistently defined in the literature, but most definitions involve a clinically significant improvement in the number of letter rows (1 or 2 rows) a patient can read on the logMAR chart, i.e., a logMAR improvement of ≥ 0.1. A review of LHON collated the following estimates of the proportion of patients who experience spontaneous visual recovery:[5]

- m.11778G>A: 14% (all age groups), 11% (aged 15 and over);
- m.14484T>C: 37% to 64%;
- m.3460G>A: 15% to 25%.

The review authors highlighted clinical consensus that the m.3460G>A is the genotype with the lowest long-term probability of recovery, and the m.14484T>C genotype is associated with a milder disease and highest probability of spontaneous recovery.[5] This is supported by a VF-14 survey, which reported median VF-14 scores of <20 for people with either a m.11778G>A or m.3460G>A mutation, but a median VF-14 score of >40 for people with an m.14484T>C genotype.

Figure 3. Characteristics associated with LHON genotypes m.11778G>A, m.3460G>A and m.14484T>C

Genotype	Estimated prevalence, international	Estimated prevalence, England	Reported rates of spontaneous recovery	VF-14, median (IQR)
Source	Poincenot *et al.* 2023 (N=1512)[4]	Poincenot *et al.* 2023 (N=139)[4]	Yu-Wai-Man and Chinnery 2021[5]	Kirkman *et al.* 2009[19]*
m.11778G>A	69%	64%	14%	16.7 (9.1 to 29.0)
m.3460G>A	13%	27%	15% to 25%	15.1 (8.1 to 29.3)
m.14484T>C	17%	8%	37% to 64%	43.8 (23.1 to 59.1)

Abbreviations: IQR, interquartile range
*Data digitised by the EAG

The EAG's clinical experts highlighted that other key prognostic factors include:

- Age at symptom onset, with children having a higher rate of spontaneous recovery than adults;[13]
- VA at baseline or nadir, with a less severe early reduction in VA being associated with better long-term prognosis.[20]

2.2.3 Current treatment pathway for LHON

Currently, there are no therapies with marketing authorisation that treat the underlying cause of LHON. Established clinical management for LHON in the National Health Service (NHS) is limited to supportive measures, which include:

- Lifestyle management guidance, including avoiding behaviours that may trigger or exacerbate LHON, such as excessive drinking or smoking;[21]
- Genetic counselling;
- Low vision aids such as magnifiers;
- Occupational and low vision rehabilitation, including optimising features of the home to facilitate use by individuals who are sight impaired.

The EAG's clinical experts noted that further support, such as assistance dogs and technology such as tablets may be provided through the support of charities but are not routinely provided by the NHS.

The EAG notes that there is a large unmet need for people with LHON, and the EAG's clinical experts agreed with the company's clinical experts that treating an individual with confirmed LHON as soon as possible is desirable. This is in-line with the 2017 International Consensus Statement on the Clinical and Therapeutic Management of Leber Hereditary Optic Neuropathy, which stated that: "Idebenone should be started as soon as possible at 900 mg/day in patients with disease less than 1 year."[13] The EAG's clinical experts also noted that they would consider treating with idebenone in the prevalent population many years after diagnosis, should idebenone be available through routine commissioning.

2.3 Critique of the company's definition of the decision problem

A summary of the final scope issued by NICE, together with the company's rationale for any deviation from this, is provided in Table 9. The EAG considers the CS to generally be in-line with the final scope issued by NICE. However, the EAG notes that the clinical efficacy and effectiveness data in the evidence submission comes from patients who had < 5 years since LHON symptom onset. The EAG is concerned that the data from such patients may have limited generalisability to the proportion of the prevalent LHON population in England who have disease duration > 5 years.

Table 9. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	People aged 12 years and older with Leber's hereditary optic neuropathy (LHON)	As per NICE scope	N/A	The EAG considers the population included in the company Submission (CS) to be largely in line with the NICE final scope. The EAG notes that the clinical evidence available is for people with onset of visual loss of ≤5 years before baseline. The EAG is concerned that the population in the current evidence may overestimate the treatment effectiveness of idebenone in individuals whose symptom onset is >5 years ago. See Section 2.3.1 below for further discussion.
Intervention	Idebenone	As per NICE scope	N/A	The treatment regimen for idebenone in the economic model and the main sources of clinical evidence are consistent with the marketing authorisation for idebenone.[22] See Section 2.3.2 below for further discussion.
Comparator	Established clinical management without idebenone including: • Visual aids. • Occupational and low vision rehabilitation.	As per NICE scope	As per NICE scope	The EAG's clinical experts confirmed that established clinical management without idebenone matches the NICE final scope and established clinical management as described in the CS.

	• Lifestyle management (no smoking, reduced alcohol consumption, diet that includes fresh fruit and vegetables).			The EAG notes that current established clinical management for LHON: does not include any active treatment; does not address the underlying cause of LHON; and does not prevent vision loss or facilitate the recovery of visual functioning. See Section 2.3.3 below for further discussion.
Outcomes	The outcome measures to be considered include: • Visual acuity (VA) • Contrast sensitivity • Retinal nerve fibre layer • Visual field assessment • Adverse effects of treatment • Health-related quality of life	The outcome measures included are: • VA • Contrast sensitivity • Retinal nerve fibre layer • Visual field assessment • Adverse effects of treatment • Health-related quality of life	As per NICE scope	The EAG notes that the company has presented clinical evidence relevant each of the outcomes specified in the NICE final scope. The outcomes used in the economic model are: • Visual acuity (change in best VA/logMAR measurements); and • Health-related quality of life (HRQoL). The EAG agrees that change in best VA is the most relevant clinical effectiveness outcome to include in the economic model. See Section 2.3.4 below for further discussion.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in	The company is broadly aligned with the overview of the economic analysis outlined in the final scope, except for the cost-	Brown et al. (1999) demonstrated that a patient's quality of life is attributed more by the better-seeing eye than	The EAG notes that results of the economic analysis are expressed in term of an incremental cost per quality-adjusted life years and with the

	terms of incremental cost per quality-adjusted life-year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account. The cost-effectiveness analysis should include consideration of the benefit in the best- and worst-seeing eye.	effectiveness analysis, which includes consideration of the benefits in the best- and worst-seeing eye. The cost-effectiveness analysis will only include consideration of the benefit in the best-seeing eye as logMAR VA is measured in the better-seeing eye rather than the worst-seeing eye.	the worst-seeing eye.[23] The better-seeing eye has a higher predictability and consistency when measuring quality of life compared to the worst-seeing eye.[23] Furthermore, change in best VA was the main secondary endpoint in the RHODOS trial. It was considered to be the endpoint most relevant to clinical practice and the one that best reflects the impact of the disease on a patient, being the closest related to visual function in daily life.[24, 25] Furthermore, during protocol assistance the CHMP agreed with the rational for including this endpoint and that it may be more clinically relevant than the primary endpoint analysis (best recovery of logMAR VA between baseline and Week 24). This also aligns with the health technology assessments of idebenone in Wales and Scotland, both of which focused on change in best VA and were granted national reimbursement for patients with LHON.[26, 27]	treatment effect being informed with better seeing eye logMAR VA as described in the NICE final scope and decision problem.

Subgroups to be considered	If the evidence allows the subgroups of people with recent vision loss will be considered.	Within B.2 of the CS, clinical data is presented split by logarithmic minimum angle of resolution (logMAR) score, disease mutation or by acute and chronic patients.	As per NICE scope.	In addition to the subgroup of people with recent vision loss included in the NICE final scope, the EAG considers the following subgroups to potentially impact clinical effectiveness: • Baseline VA (logMAR <1 at baseline vs logMAR ≥1); and • LHON genotype. See Section 2.3.5 below for further discussion; the results of subgroup analyses from the primary sources of clinical evidence are presented in Section 3.3.
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	There are no special considerations relating to issues of equity or equality.	N/A	The EAG notes that idebenone has been available via routine commissioning in Wales since March 2021.[26]

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; CS. Company Submission; EAG, External Assessment Group; HRQoL, Health related quality of life; LHON, Leber's hereditary optic neuropathy; logMAR, logarithm of the minimum angle of resolution; NICE, National Institute for Health and Care Excellence; VA, visual acuity

2.3.1 Population

The EAG considers the population considered in the CS to be in-line with the NICE final scope: people with LHON aged 12 years and over. The clinical efficacy and effectiveness used in the company's economic model came from one RCT (RHODOS) and two real-world evidence studies (Expanded access program [EAP] and the Case record survey [CaRS-I]). Further clinical evidence was presented from the LEROS clinical trial and Case record survey II (CaRS-II).

The EAG considers populations from each of the clinical trials and real-world evidence sources to be largely consistent with the NICE final scope (See Section 3.2 for further discussion). However, the EAG notes that while idebenone is positioned for all individuals with LHON aged ≥12 years, the studies providing clinical evidence only included individuals for who the onset of visual loss was ≤5 years at baseline. Specifically, the following inclusion criteria were used in each study:

- RHODOS: Age ≥ 14 years and <65 years, impaired VA in at least one eye due to LHON, onset of visual loss due to LHON was 5 years or less prior to baseline, confirmation of either m.11778G>A; m.14484T>C; or m.3460G>A mtDNA mutations at >60% in blood, no explanation for the visual failure besides LHON;
- EAP: confirmation of any of the three major LHON-causative mtDNA mutations and onset of vision loss in the most recently affected eye less than 12 months prior to the date of the Baseline visit;
- LEROS: patients with a diagnosis of LHON, aged ≥12 years and with onset of symptoms within ≤5 years prior to Baseline;
- CaRS-I: historical case record data from LHON patients (with molecular diagnosis), from 11 participating clinical centres; included all patients with no record of idebenone use, whose case records were not previously included in the RHODOS or EAP datasets, where one of the three major LHON-causative mutations was carried, where the date of onset of symptoms in the first affected eye was known and where Presentation was ≤24 months of Onset.
- CaRS-II: historical case record data from LHON patients from 20 sites located in 7 countries; included patients aged ≥12 years, whose onset of symptoms dated after 1999 and was 'well documented' (at least the month of the onset of symptoms was known for each eye), with at least two VA assessments available within 5 years of onset of symptoms and prior to idebenone use, with a genetic diagnosis for LHON for one of the following mtDNA mutations

m.11778G>A; m.14484T>C; and m.3460G>A, with no participation in an interventional clinical trial after the onset of symptoms.

The EAG notes that time since symptom onset is an important prognostic factor for people with LHON. The likelihood of spontaneous recovery is greater early on, i.e. in the dynamic phase in the disease, and the EAG notes irreversible damage to the optic nerve may be established over time, limiting the potential for recovery for patients with longer disease durations.[5] Hence, the EAG has concerns that the population in the current evidence may overestimate the treatment effect of idebenone in the prevalent population with LHON in England, a large part of which is expected to have disease onset > 5 years ago.

EAG clinical experts advised the EAG that genotype is also an important prognostic factor for people with LHON. The EAG notes that the populations included in the clinical evidence were limited to people with the 3 most prevalent genotypes m.11778G>A, m.14484T>C or m.3460G>A. However, the EAG considers that these are representative of the vast majority of patients in England and thus has no concerns that the treatment effect of idebenone is likely to differ.

The EAG also notes that while the population in the NICE final scope is people with LHON aged 12 years and over, patients younger than 14 years were excluded in the RHODOS RCT. However, the EAG considers it reasonable to assume that the safety and efficacy of idebenone observed in the clinical trials would generalise to these patients.

In the economic model, the baseline characteristics of the patient cohort were based on the RHODOS trial. As such, a patient mean of age of 34 at baseline was assumed, with 14% of the population being female.

2.3.2 Intervention

Idebenone (Raxone®), a short-chain benzoquinone, is an antioxidant that as outlined in Table 2 of the CS is thought to re-activate viable-but-inactive retinal ganglion cells (RGCs) in LHON patients by restoring cellular energy (ATP) generation.[28] Idebenone has a marketing authorisation for the treatment of visual impairment in adults and adolescents aged 12 years and over with LHON.[29]

This indication is consistent with the company Submission for this NICE single technology appraisal (ID547). Idebenone is available as 150 mg film-coated tablets, and the recommended dose is 900

mg/day (two tablets, 3 times a day), to be taken with food.[28] No additional tests or investigations are required. Patients should be regularly monitored according to local clinical practice.[28]

Although the duration of treatment is not specified in the SmPC, the company has assumed that patients would continue treatment for up to a maximum of three years. This aligns with the length of follow-up data available from the clinical evidence. EAG clinical experts have confirmed that this is a reasonable assumption but highlighted that patients could be reluctant to stop taking idebenone if they have experienced a benefit from treatment and there is currently very limited evidence demonstrating what happens after treatment discontinuation.

The EAG considers that the dosing regimen of idebenone in the RHODOS trial, the EAP and the LEROS trial to be consistent with its marketing authorisation, with idebenone administered orally at a dose of 300mg (2 x 150mg) three times a day (total daily dose 900mg).

2.3.3 Comparators

The comparator listed in the final scope issued by NICE was established clinical management without idebenone, which includes:

- Visual aids;
- Occupational and low vision rehabilitation;
- Lifestyle management (no smoking, reduced alcohol consumption, diet that includes fresh fruit and vegetables).

As discussed in Section 2.2, there is currently no active treatment tackling the underlying genetic condition of LHON, and patients are currently managed with standard of care (SoC). Within this framework, idebenone potentially presents a step change in the management of LHON. The EAG's clinical experts confirmed established clinical management options without idebenone match the options listed in the NICE final scope and described in the CS; current supportive options included in the SoC do not prevent vision loss or allow recovery of visual functioning. As such, SoC was the only comparator to idebenone in the cost effectiveness model.

In the clinical trials and real-world evidence used to inform the CS, idebenone was compared to placebo or no treatment but established clinical management without idebenone as described in the NICE final scope is available to all LHON patients by default.

2.3.4 Outcomes

The EAG notes that the company has submitted evidence relevant to each of the outcomes specified in the NICE final scope. The clinical outcome used in the economic model is the change in a patient's best VA, which is applied as transition probabilities between logMAR categories for every three months of treatment.

The EAG considers a key difference between the decision problem specified by the company and the NICE final scope is in the endpoint considered in the cost-effectiveness analysis as the company only included consideration of the benefit in the best-seeing eye as logMAR VA is measured in the better-seeing eye rather than also including consideration of the benefit in the worst seeing eye as specified in the NICE final scope. While change in best VA was not the primary outcome of the RHODOS trial, the EAG agrees that change in best VA is the most clinically relevant outcome: the EAG's clinical experts highlighted that a patient's quality of life is primarily driven by the VA of their best seeing eye.

The EAG notes that the company has provided analyses for many outcomes both at the level of the individual eye (e.g. change in logMAR VA of individual eyes) and at the level of the patient (e.g. change logMAR VA of a patient's best eye), and the EAG notes that the treatment effect of idebenone is consistent between each level of analysis.

2.3.5 Subgroups/special considerations

The EAG notes that several baseline characteristics of people with LHON are meaningful prognostic factors and/or treatment effect modifiers. These include:

- LHON genotype:
    - As outlined in Section 2.2.2, the m.14484T>C genotype is associated with a milder disease and higher probability of spontaneous recovery than the m.11778G>A and m.3460G>A genotypes;
- Time since symptom onset:
    - The EAG's clinical experts noted that the treatment effect of idebenone could plausibly be greater for incident patients treated before reaching nadir, although published evidence has mostly been on patients in the dynamic/early chronic phase of the disease;
- VA at baseline or nadir:

- The EAG's clinical experts noted that the long-term possibility of recovering sight will be related to a patient's baseline or worst VA, with meaningful recovery being less likely for patients with worse VA at nadir. The EAG notes this subgroup was used as the basis for a restricted recommendation for idebenone for use within NHS Scotland: patients with LHON who are not yet blind i.e., who do not meet the UK criteria to be registered as severely sight impaired.[27]

The EAG notes that while outcome data are available for each of these subgroups (presented in Section 3.3.4), the limited sample size within each subgroup leads to a high degree of uncertainty in the comparisons.

3 Clinical effectiveness

3.1 Critique of the methods of the review

The company conducted two systematic literature reviews (SLRs) which were presented in Appendix D of the company Submission (CS):

- A clinical SLR that aimed to identify all randomised controlled trials (RCTs) and interventional studies reporting on the clinical efficacy and safety of idebenone and other treatments for LHON;
- A real-world evidence SLR aiming to identify any real-world evidence reporting on the clinical effectiveness and safety of idebenone and other treatments for LHON.

The EAG notes the SLRs were not limited by intervention or comparator, and studies of comparators not relevant to the current appraisal were included throughout. The EAG considered all other eligibility criteria of the SLR to appropriately reflect the final scope as issued by NICE, although studies of no pharmacological intervention (i.e., current SoC) were excluded from the real-world evidence SLR. The EAG is concerned that non-interventional studies were excluded from the real-world evidence review as the comparator for idebenone in the current appraisal is no intervention. This includes the company's own preferred source of long-term data for the comparator cohort in the economic model, the Case Record Survey (CaRS-I) and Case Record Survey II (CaRS-II), which "were excluded from the SLR due to their non-interventional nature, which falls outside the SLR criteria." (CS, page 31). Table 10 provides an overview of the EAG's critique of the company SLRs.

Table 10. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Search Dates	Appendix D1.1.3	**Appropriate** • The primary database searches were conducted on 25 February 2022 and updated on 10 March 2023.
Data sources	Appendix D1.1.3	**Appropriate** • A range of electronic databases were searched, including Embase and MEDLINE, Econlit and a comprehensive search of EBMR; • An appropriate range of conference proceedings were searched between January 2019 and February 2023, detailed in Table 7 of the CS;

		• Nine HTA body websites were searched, and presented in Table 8 of Appendix D; • Ongoing trials were identified through a search of clinicaltrials.gov. The EAG notes that separate searches of EUCTR or WHO ITPR were not reported, but the EAG considers it unlikely any key ongoing trails would have been missed considering the pivotal trials of idebenone was first published in 2011. To verify this, the EAG conducted a search of EUCTR on 20 November 2023 using the key words "LHON" and "Optic neuropathy". These two searches did not identify any relevant data beyond that already identified by the company's SLR.
Search strategies	Appendix D1.1.3 Table 5 and Table 6	**Appropriate** • The EAG considers the search strategies reported in Appendix D to be likely to detect all studies relevant to the current appraisal.
Inclusion criteria	Appendix D1.1.2	**Clinical SLR: Appropriate** • The EAG considers the eligibility criteria to be broader than necessary to identify all clinical trials relevant to final scope issued by NICE. **Real world evidence SLR: Large concerns** • The EAG is concerned that non-interventional studies were excluded from the real-world evidence SLR, but the comparator in the current appraisal is no intervention. The EAG notes that studies not reported in the English language were excluded from both reviews.
Screening	Appendix D1.1.4	**Appropriate** • Screening was performed by two independent reviews at both the title and abstract, and full text, appraisal stages.
Data extraction	Appendix D.1.1.5	**Appropriate** • Data were extracted by a single reviewer and checked for accuracy by a second reviewer.
Tool for quality assessment of included study or studies	Appendix D1.1.5	**Some concerns** • The company used the NICE checklist for RCTs to assess the quality of included RCTs, and the ROBINS-I checklist to assess the quality of included non-randomised studies. The EAG considered these checklists to be appropriate; • Free-text justifications for each quality assessment decision were not reported, which made it difficult to assess the quality and validity of the risk of bias assessments for each study.

Abbreviations: CS, company submission; EAG, External Assessment Group; EBMR, Evidence-Based Medicine Reviews; EUCTR, EU Clinical Trials Register; HTA, health technology assessment; ITT, intent-to-treat; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial; ROBINS-I, Risk Of Bias In Non-Randomised Studies - of Interventions; SLR, systematic literature review; WHO ICTRP, World Health Organisation International Clinical Trials Registry Platform.

In the clinical SLR, a total of 1,408 records were identified in the database searches. Following de-duplication (n=268), exclusions of non-human (N=132) and non-English language (N=77) records, 931

records entered the title and abstract appraisal. Of these, 162 records were selected for full-text appraisal, and 35 records were included. A further 23 records were identified through conference and bibliography searches, leading to 58 records from 16 clinical studies being included in the clinical SLR. The clinical trials investigated the following interventions: idebenone (N=3); rAAV2/2-ND4 gene therapy (N=6); EPI-743 (N=2); cyclosporine (N=1); brimonidine purite 0.15% (N=1); skin electrical stimulation (N=1); elamipretide 1% (N=1); and visomitin (N=1). The three idebenone clinical trials subsequently included in the CS were:

- RHODOS: a Phase 2 RCT comparing idebenone (n=55) with placebo (n=30) over 24 weeks of treatment. An observational follow-up visit (RHODOS OFU) was available for N=58 patients, a median of 30 months after the RHODOS Week 24 visit. RHODOS was conducted at sites in England, The Netherlands and Germany;[25]
- LEROS: a Phase 4 single arm study of idebenone (n=181) over a 24-month treatment period. An observational natural history cohort (n=372) was constructed for comparison. LEROS was conducted across 11 countries, including England, Wales, the USA and eight EU nations;[30]
- UMIN000017939: a single arm clinical trial of idebenone (n=57) over 24 weeks of treatment. UMIN000017939 was conducted in Japan.[31]

In the real-world evidence SLR a total of 1,490 records were identified in the database searches. Following de-duplication (n=286), exclusions of non-human (N=81) and non-English language (N=78) records, 1,045 records entered the title and abstract appraisal. Of these, 249 records were selected for full-text appraisal, and 28 records were included. A further 8 records were identified through conference and bibliography searches, leading to 36 records from 22 real world evidence studies being included in the real-world evidence SLR. Twenty of these studies were studies of idebenone alone (N=18) or in combination with vitamin therapy (N=2), one study examined rAAV2 ND4 gene therapy, and one study was of low vision devices. Following clarification, two further studies that were originally excluded from the SLR were re-included, but were not deemed relevant to the CS. The company's updated PRISMA diagram is presented in Figure 3 of Appendix 1 of the company response to clarification.

At clarification, the company stated they considered studies from the real-world evidence SLR for inclusion in the economic modelling based on "various factors such as geographical population, gender proportion, study design, intervention type, and sample size". From this, the Expanded Access Programme (EAP) was identified as "the most robust, being the only multicentre study with

UK patients and one of the largest sample sizes." Reasons for the exclusion of other real-world evidence studies of interventions for LHON were presented in Table 2 of the clarification response. The EAG agrees that the EAP is the most relevant real-world data source of the identified studies. While the EAG considered it plausible to exclude studies such as Van Everdingen 2022,[32] a retrospective multicentre study of idebenone in the Netherlands, could contain relevant data, the study did not report the individual participant transition probabilities between logMAR states that would be required for inclusion in the economic model.

While only one study was identified in the real-world evidence SLR, the company used data from three real world evidence sources in the economic modelling:

- Expanded Access Program (EAP): a retrospective analysis of 111 patients treated with idebenone. Records associated with the EAP were included in the real-world evidence SLR. The EAP was conducted in sites from the UK, Germany, Australia, New Zealand, Poland, Sweden, Spain, Turkey, Switzerland and the USA, and included patients with an onset of vision loss less than 12 months prior to initiating with idebenone only;[33]
- Case Record Survey (CaRS-I) and Case Record Survey II (CaRS-II): retrospective, observational studies of medical records of patients with a genetically confirmed diagnosis of LHON. Both were international studies, and the company explained that only results from the CaRS-I study were available at the time of the submission. The company provided the CSR for CaRS-II following the EAG's clarification questions. CaRS-I reported natural history data for 106 LHON patients;[34] CaRS-II reported natural history data for 219 patients.[35]
- PAROS: a post-authorisation safety study with idebenone due to be published in Q2 2024. Upon request from the EAG, the company provided the clinical study report (CSR) of PAROS, although the EAG notes that data from PAROS are not included in the CS.[36]

3.2 Critique of trials of the technology of interest

In the CS, three studies were presented containing evidence of the clinical efficacy and effectiveness of idebenone. The RHODOS RCT (N=85) comprised the main source of clinical evidence for the efficacy of idebenone up to 6 months (24 weeks),[37] whereas the LEROS Phase IV clinical trial (N=199) and EAP (N=111) provided data on the long-term effectiveness of idebenone for LHON.[38, 39] Data informing the disease course of LHON under established clinical management were presented up to 6 months from the placebo arm of RHODOS, and longer-term data were presented from CaRS-I and CaRS-II: retrospective, observational natural history studies of patients with LHON.[34, 35] The EAG now

presents a critique of the design and conduct of RHODOS, LEROS, the EAP and the CaRS-I and CaRS-II natural history studies.

3.2.1 RHODOS

RHODOS (NCT00747487), was a randomised, double-blind, placebo-controlled multicentre phase II trial, evaluating the efficacy and safety of idebenone in adolescent and adult patients aged ≥14 to <65 years with impaired VA in at least one eye due to LHON with onset of visual loss ≤5 years and a confirmation of diagnosis by identification of either m.11778G>A, m.14484T>C or m.3460G>A LHON mtDNA mutations. A single observational follow-up visit at median time of 30 months (range: 20.9 to 42.5 months; 131 weeks) was performed providing further follow-up data from N=58 participants of the original RHODOS trial. This included patients who previously participated in the RHODOS trial in both the idebenone and placebo arms, but who were not expected to receive idebenone treatment following the completion of RHODOS.

The EAG considered RHODOS to be a high quality RCT with appropriate randomisation, and blinding procedures. However, the EAG notes it was a phase II design with a relatively small population of people at various stages of disease progression and with a short follow-up providing limited evidence on the long-term effect of idebenone therapy. Thus, results should be treated with caution.

The EAG's assessment of the design, conduct, internal validity of the RHODOS trial is presented in Table 11 below.

Table 11. EAG's summary of the design, conduct and analysis of RHODOS

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	Section B.2.3.1 in CS and RHODOS CSR	**Appropriate** Patients were randomised in a 2:1 ratio to idebenone 900mg/day (n=55) or placebo (n=30). Randomisation was stratified by disease history (disease onset more or less than one year prior to randomisation) and by mutation type (m.11778G>A, m.3460G>A and m.14484T>C).
Concealment of treatment allocation	RHODOS CSR	**Appropriate** In the CSR is specified: the randomisation procedure was centralised [redacted]

Eligibility criteria	Section B.2.3.1.1 in CS	**Appropriate but limited to people with onset of vision loss ≤5 years prior to baseline.** Full details of the eligibility criteria for the RHODOS trial population are available in the CS Table 6. Key inclusion criteria were: • Age ≥ 14 years and <65 years; • Impaired VA in at least one eye due to LHON; • Onset of visual loss due to LHON was 5 years or less prior to baseline; • Confirmation of either m.11778G>A, m.14484T>C or m.3460G>A LHON mtDNA mutations at >60% in blood; • no explanation for the visual failure besides LHON. The EAG notes that a considerable proportion of the prevalent LHON population in England will have LHON onset > 5 years ago. Hence, RHODOS trial population may not be representative of the whole spectrum of LHON patients likely to be eligible for idebenone in UK clinical practice.
Blinding	Section B.2.3.1 in CS	**Appropriate** RHODOS was a double-blind, placebo controlled RCT with patients and any people involved in the study (including investigators, site staff, sponsor, and care provider) blinded to study treatment.
Baseline characteristics	Section B.2.3.2.2 in CS	**Appropriate** The EAG's clinical experts noted that participants' length of time since symptom onset, their baseline logMAR as well as the proportion of patients with onset of symptoms >1 year, suggest the population of the RHODOS trial was most likely representative of prevalent LHON patients at the chronic phase of the disease and less likely the earlier subacute/acute and dynamic phases.
Dropouts	RHODOS CSR	**Appropriate** In the CSR, it is reported that "of the 85 patients randomised and treated, 7 patients discontinued the study prematurely, 3 patients (5.5%) treated with idebenone, and 4 patients (13.3%) treated with placebo." The most commonly reported reason for premature discontinuation was withdrawal of consent (2 patients treated with idebenone and 1 patient treated with placebo). One patient in each treatment group was withdrawn due to adverse events." Considering the number of discontinuations and the reasons for discontinuation in each group, the EAG is not concerned about the potential impact of discontinuation in the RHODOS trial upon the results.
Outcome assessment	Section B.2.3.3.2	**Efficacy and safety: Appropriate** **Health related quality of life: Some concerns** Changes in VA were measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) logMAR chart following the prespecified clinical trial protocol. The EAG notes that [redacted], but the EAG considers logMAR measured by ETDRS charts to be a valid endpoint.

		The primary endpoint of RHODOS was the best recovery of logMAR visual acuity in either right or left eye; however, the EAG considers the secondary endpoint, the change in best VA, to be the most clinically relevant endpoint. The EAG notes that these analyses are different analyses of the same fundamental measurement – logMAR score. Quality of life was assessed in RHODOS using the VF-14 questionnaire, which may have poor psychometric validity in LHON patients (see Section 2.2).
Statistical analysis		
Sample size and power	Section B.2.4.1.2.2 in CS	**Some concerns** The company reported that based on VA change of -0.05±0.3 logMAR in the placebo group and -0.25 ±0.3 logMAR in the idebenone group in the ITT population and with the proportion of patients receiving idebenone and placebo of 2:1, 84 patients were estimated to provide 80% statistical power to reject the null hypothesis of no difference in VA change between the two groups. No justification was provided for the VA change by Week 24 in either the placebo or idebenone arms assumed in the power calculation. The EAG agrees with the company's conclusion that 24 weeks "may not have been long enough to fully assess the benefit of idebenone" and considers it likely that a larger sample size with a longer follow-up would be required to allow for a minimum clinically important change in VA to be detected.
Handling of missing data	Section B.2.4.1.2.3. in CS	**Reasonable** Missing data were handled using a Mixed-Model for Repeated Measures (MMRM), assuming data are missing at random. This utilised the observed data to make inferences based on the multivariate normal distribution, with parameters estimated from the available data.
Analysis sets	Section B.2.4.1 in CS	**Some concerns** The ITT population (n=82) included all randomised patients who received at least one dose of the study medication, [redacted] The mITT population (n=81) was the same as the ITT population, but for VA and colour contrast analyses, one patient randomised to placebo, who was identified as a natural history confounder due to ongoing spontaneous recovery of vision at the time of randomisation was excluded. The EAG is concerned that the exclusion of the patient that was considered a natural history confounder in the mITT population biases the efficacy results in favour of idebenone.

Abbreviations: CS, company submission; CSR, clinical study report; EAG, External Assessment Group; ETDRS, Early Treatment Diabetic Retinopathy Study; ITT, intent-to-treat; LHON, Leber's hereditary optic neuropathy; logMAR, logarithm of the minimum angle of resolution; mITT, modified intent-to-treat; MMRM, Mixed-Model for Repeated Measures; RCT, randomised controlled trial; VA, visual acuity VF, visual function.

3.2.2 RHODOS-OFU

In RHODOS-OFU,[40] the long-term follow-up study of RHODOS, patients (n=58) previously randomised to idebenone (n=39) or placebo (n=19) in RHODOS (as described in Table 11), received no treatment. However, there were five patients from the total efficacy population (three from the idebenone group and two from the placebo group) who reported use of idebenone between Week 24 of RHODOS and the RHODOS-OFU single visit (median 30 months, range: 20.9 to 42.5 months). The dose used was not provided in all cases, although three patients reported the use of 900 mg/day. The sub-population recruited to RHODOS-OFU was representative of the RHODOS study population and there were no significant differences with the original RHODOS cohort. However, the EAG notes that the number of patients included in the RHODOS-OFU visit was lower than that included in the original RHODOS trial and the proportion of patients from the original sample included in RHODOS-OFU also differed between the idebenone (73.6%) and the SoC (65.5%) groups. Thus, the EAG has concerns this may indicate selection bias in the inclusion of patients in the RHODOS-OFU trial, considering that patients responding to treatment in the RHODOS trial would be more likely to complete the trial and be willing to participate in the RHODOS-OFU. As a result, the EAG notes that potential selection bias in the RHODOS-OFU visit data favouring idebenone, may overestimate the long-term treatment effect of idebenone compared to SoC (See Section 3.4.4.).

3.2.3 EAP and LEROS

The EAP and LEROS studies provide data on the clinical effectiveness of long-term treatment of LHON with idebenone.

The EAP (N=111) was an open-label, multicentre retrospective, non-controlled analysis of long-term VA and safety in LHON patients treated with idebenone (treatment duration up to 36 months) with onset of vision loss in the second eye less than 12 months prior to the date of the baseline visit. Follow-up time in the EAP ranged between 2.4 and 70.4 months. Patients were seen and followed up after initiating of treatment with idebenone, according to local practice. VA assessments were conducted at regular (generally 3-monthly clinical visits).

LEROS (N=199) was an external natural history controlled open-label, phase IV intervention study assessing the efficacy and safety of long-term treatment with idebenone in adolescent and adult

patients with LHON. LEROS had a 24-month treatment period with visits taking “place at Month 1, Month 3, Month 6, Month 9, Month 12, Month 18 and Month 24”.

The EAG presents a critique of the design and conduct of the EAP and LEROS trial in Table 12, for the idebenone treated patients. The EAG provides a separate critique of the natural history matched-controlled analyses from LEROS, the only statistical analyses presented by the company comparing long-term idebenone treatment with SoC, in Section 3.4.

Table 12. EAG's summary of the design, conduct and analysis of EAP and the LEROS trial

Aspect of trial design or conduct	EAP	LEROS
Randomisation, blinding and concealment of treatment allocation	**N/A** Given the EAP was a real-world, open-label non-controlled analysis, there was no randomisation procedure and blinding, and concealment of allocation were not applicable.	**N/A** Given LEROS was a natural history controlled study of patients treated with idebenone with no enrolled comparator group, there was no randomisation procedure and blinding, and concealment of allocation were not applicable.
Eligibility criteria	**Appropriate but not representative of prevalent population eligible for idebenone in UK clinical practice.** Full details of the eligibility criteria for the EAP population are available in B.2.3.5.2 in the CS and the EAP CSR. Key inclusion criteria were: • A confirmed mtDNA LHON mutation; • Onset of symptoms in the most recently affected eye within 1 year before enrolment. Since the EAP was restricted to patients with onset of vision loss of less than 12 months in the most recently affected eye, the EAG notes it included a population at an earlier stage of disease progression, than RHODOS, LEROS and the prevalent population in England. Thus, the EAG considers EAP patients to be more representative of the incident population of patients with LHON but not the prevalent population forming a large part of clinical practice in the UK.	**Appropriate** Full details of the eligibility criteria for the LEROS trial population are available in Appendix M, Table 2. Key inclusion criteria were: • Impaired VA in affected eyes due to LHON; • No explanation for visual loss besides LHON; • Age ≥ 12 years; • Onset of symptoms ≤ 5 years prior to baseline. Confirmation of either m.11778G>A, m.14484T>C or m.3460G>A LHON mtDNA (for the Intent-to-treat population, not required for enrolment).
Baseline characteristics	**Appropriate but reflective of an incident population with LHON** The EAG considers the baseline characteristics of the EAP to reflect a LHON population in the acute and dynamic phase of LHON, but not the chronic phase. Further discussion of the baseline characteristics of each trial are provided in Section 3.2.5.	**Appropriate** The EAG considers LEROS to contain a mixture of patients in the acute, dynamic and chronic phase of LHON. Further discussion of the baseline characteristics of each trial are provided in Section 3.2.5.

Sample size, dropouts, and long-term data availability	**Large concerns** The company reports that [redacted] In the CSR it is reported that: "… [redacted] Considering the length of follow-up was up to 36 months, the EAG notes a considerable proportion of patients discontinued or were lost to follow-up with data from a limited number of patients being available >24 months and the number of patients progressively decreasing as treatment duration increases (see Table 13 below). The limited number of patients with data available >24 months may limit the robustness of any conclusions about long-term effectiveness of idebenone.	**Appropriate/small concerns** In the CSR it is reported that: "… [redacted] Of the 199 patients enrolled in the LEROS trial, 57 had discontinued at 24 months (CSR, Figure 1). In the CSR it is reported that for the Safety population: "[redacted] The EAG notes that this indicates a considerably larger proportion of patients with data available overtime compared to the EAP. This has been confirmed in the company's response to clarification questions, with data availability for the EAP and LEROS trial displayed in Table 13 below.
Handling of missing data	**Unclear**	**Unclear** A sensitivity analysis assessing the impact of incomplete data was performed with a generalized linear mixed model. In the CSR it is reported that: "[redacted]
Outcome assessment	**Some concerns** Best-corrected visual acuity (BCVA) was "generally assessed using ETDRS logMAR charts or converted from standard Snellen notation to logMAR for analysis purposes" at 3 monthly intervals or according to the treating physician's normal clinical practice.	**Appropriate** BCVA was assessed at every visit using ETDRS logMAR charts, following detailed standardised procedures outlined in the clinical study protocol.

	The EAG notes that the study protocol only specified that "[redacted]" and the mixed recording of BCVA through ETDRS and Snellen charts likely increases the error associated with BCVA measurements in the EAP compared to RHODOS and LEROS. The EAG also notes that as visits could occur "according to the treating physician's normal clinical practice", data missingness is at a higher risk of introducing bias than when all visits are pre-specified.	
Analysis sets	The Safety population (n=111), including all patients enrolled who received at least one dose of idebenone, was used for analysis of safety information. The Efficacy population (n=87) was a sub-population of the Safety population, who carried one of the three major LHON-causative mtDNA mutations, who had time since onset at baseline of less than 12 months in the most recently affected eye, and for whom post-baseline VA efficacy data was available. All analyses for efficacy were carried out on the Efficacy population.	The Safety population (n=198), including patients who received treatment with idebenone was used for the analysis of adverse reactions. The mITT population (n=181) included all patients enrolled in LEROS who: were carriers of one of the three major LHON mtDNA mutations (m.11778G>A; m.3460G>A or m.14484T>C), had received at least one dose of the study medication and provided at least one post-baseline VA assessment. Apart from the Safety population, data were summarised by onset of symptoms (≤1 year or >1 year after onset of symptoms).

Abbreviations: AE, adverse events; BCVA, Best-corrected visual acuity; CSR, clinical study report; EAG, External Assessment Group; EAP, Expanded Access Program; ETDRS, Early Treatment Diabetic Retinopathy Study; LHON, Leber's hereditary optic neuropathy; logMAR, logarithm of the minimum angle of resolution; mITT, modified intent-to-treat; VA, visual acuity.

Table 13. Data availability in EAP and LEROS trial (adapted from Table 9 in company's clarification response)

	Months			
Patient populations	**>0**	**>6**	**>12**	**>24**
EAP EP: Patients with outcome data available N (%)	87 (100.0%)	81 (93.1%)	63 (72.4%)	42 (48.3%)
LEROS ITT: Patients with outcome data available N (%)	196 (100.0%)	171 (87.2%)	151 (77.0%)	125 (63.7%)

Abbreviations: EP, efficacy population; ITT, intent-to-treat.

The EAG notes that, although long-term follow up data spanning 36 months are available from the EAP, the number of patients for which data were available decreased with each clinic visit at a greater rate compared to the LEROS trial, with a considerable difference in the proportion of data available >24 months in favour of the LEROS trial. Thus, the EAG has concerns over the company's choice of the EAP as the preferred source of long-term effectiveness in the economic model as despite the overall length of follow-up for the EAP being longer, the availability of data was considerably lower. See Section 3.3.7 and Section 4.2.4 for further details of the EAG's critique of the company's choice of long-term effectiveness data source.

3.2.4 CaRS-I and CaRS-II

CaRS-I and CaRS-II were multi-centre, retrospective, observational, historical case record surveys of untreated patients with genetically confirmed diagnosis of LHON, providing clinical data on the natural progression of LHON. The studies were collecting historically documented VA data from existing medical records from patients who were not receiving idebenone with no comparison group, thus randomisation was not applicable. This was considered a limitation as similarly to the EAP and LEROS trials, CaRS do not provide direct comparative evidence on long-term treatment with idebenone compared to SoC. Comparative evidence had to be indirectly obtained through a matched controlled analysis of a subgroup of patients from the LEROS trial matched with a natural history group of idebenone naïve patients from data from CaRS-I and CaRS-II. See Section 3.4 for the EAG's critique of the company's matched controlled analysis.

CaRS-I (n=383) collected historical case record data from LHON patients (with genetically confirmed diagnosis), from 11 participating clinical centres; no exclusion criteria were specified, and data were collected without pre-selection, based on participating clinical centres record-keeping practices.

CaRS-II (n=219) collected data from patients with a genetically confirmed diagnosis of LHON who fulfilled the following prospectively defined inclusion criteria:

- Age≥12 years;
- The onset of symptoms was dated after 1999 and was well documented (at least the month of the onset of symptoms was known for each eye);
- At least two VA assessments were available within 5 years of onset of symptoms and prior to idebenone use;
- Have a genetic diagnosis for LHON for one of the following mtDNA mutations: m.11778G>A; m.3460G>A or m.14484T>C.

[redacted]In the CSR of CARS-I, it is noted that the studies [redacted]The EAG has concerns about the robustness of data from CaRS, considering it was a retrospective review of medical records with a large proportion of missing data and a high degree of variability in the availability of data from different patients at different time points. Thus, reliable conclusions about the natural course of VA changes in LHON cannot be drawn.

3.2.5 Trial baseline characteristics

The EAG noted that the baseline characteristics reported across studies included in the CS differed, making it difficult to assess the similarity between the populations. Thus, the EAG requested that the company provide baseline characteristics for each study consistently in a single table. In response to the EAG's request the company provided the following.

Table 14. Baseline characteristics across studies (adapted from Table 7 in the company's initial clarification response)

	RHODOS		EAP		LEROS		CaRS I		CaRS II	
Characteristic	Idebenone N=55 (N=53 ITT population)	Placebo N=30 (N=29 ITT population)	LHON population N=105	Efficacy population N=87	ITT N=196	NH matched comparator N=106	Natural history population N=106	Natural history outcomes population N=74	Natural history population N=219	Natural history outcomes population N=219
Age, mean ± SD [median] (range) (years)	33.8 ± 14.8 [30.0] (14–63)	33.6 ± 14.6 [28.5] (14–66)	31.7±18.5 [23.6] (6.9–80.1)	31.9±17.4 [24.6] (6.9–80.1)	34.1 ± 15.2 [31.9] (12.1–79.2)	32.1 ± 14.5 [28.0] (13.0–75.0)	32.4 (15.5) [29.5] (6 – 79)	31.1 ± 14.6 (7 – 75)	30.0±15.0 [26.0] (6-68)	30.0±15.0 [26.0] (6-68)
Male, n (%)	47 (85.5)	26 (86.7)	82 (78.1%)	71 (81.6%)	[redacted]	88 (83.0)	85 (80.2)	61 (82.4)	175 (79.9)	175 (79.9)
Age at symptom onset mean ± SD [median] (range) (years)	NR	NR	30.8±18.5 [23.0] (6.6 - 78.9)	31.4±17.3 [24.2] (6.6 - 78.9)	32.5 ± 15.2 [30.4] (8.8 – 78.2)	31.7 ± 14.5 [28] (13.0 – 75.0)	32.1 ± 15.4 [29.5] (6 – 78)	30.9 ± 14.6 (7 – 75)	29.8±15.0 [26.0] (6-68)	29.8±15.0 [26.0] (6-68)
Age at diagnosis mean ± SD [median]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Race, n (%)										

	RHODOS		EAP		LEROS		CaRS I		CaRS II	
Caucasian/white	53 (96.4)	30 (100)	NR	NR	54 (27.6)	NR	NR	NR	NR	NR
Black	1 (1.8)	0	NR	NR	8 (4.1)	NR	NR	NR	NR	NR
Other	1 (1.8)	0	NR	NR	134 (68.4)	NR	NR	NR	NR	NR
Mutations, n (%)										
m.11778G>A	37 (67.3)	20 (66.7)	61 (58.1)	54 (62.1)	[redacted]	77 (72.6)	78 (73.6)	55 (74.3)	157 (71.7)	157 (71.7)
m.14484T>C	11 (20.0)	6 (20.0)	17 (16.2)	16 (18.4)	[redacted]	12 (11.3)	11 (10.4)	7 (9.5)	32 (14.6)	32 (14.6)
m.3460G>A	7 (12.7)	4 (13.3)	18 (17.1)	17 (19.5)	[redacted]	17 (16.0)	17 (16.0)	12 (16.2)	30 (13.7)	30 (13.7)
Other	-	-	2 (1.9)	-	[redacted]	-	-	-	-	-
Negative	-	-	-	-	[redacted]	-	-	-	-	-
Months since onset of vision loss, mean ± SD [median] (range)	22.8 ± 16.2 [17.8] (3–62)	23.7 ± 16.4 [19.2] (2–57)	10.6±18.7 [5.6] (0.9 - 133.7)	6.2±3.7 [5.0] (0.9 - 16.7)	18.4±15.8 [12.3] (0.3-58.3)	NR	Years: 0.3±0.4 [0.2] (0.0– 1.9)	Years: 0.3±0.4 [0.1] (0.0– 1.9)	3.4±5.6 [1.7] (0.7-3.9)	3.4±5.6 [1.7] (0.7-3.9)
Proportion of patients with nadir prior to baselines, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

	RHODOS		EAP		LEROS		CaRS I		CaRS II	
Months since nadir at baseline, mean ± SD [median] (range)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Patients with onset of symptoms >1 year, n (%)	36 (65.5)	19 (63.3)	NR	NR	87 (44.4)	NR	8 (7.5)	2 (2.7)	10 (4.6	10 (4.6)
Onset of vision loss within 1 year, n (%)	19 (34.5)	11 (36.7)	NR	NR	109 (55.6)	NR	98 (92.5)	72 (97.3)	209 (95.4)	209 (95.4)
Baseline logMAR distribution, n (%)										
One eye logMAR ≥1.0	5 (9.4)	2 (6.9)	Best VA: 70 (66.7)	Best VA: 63 (72.4)	NR	NR	NR	NR	NR	NR
Both eyes logMAR ≥1.0 (legally blind)	45 (84.9)	25 (86.2)	NR	NR	NR	NR	50 (47.1)	27 (36.5)	82 (37.7)	82 (37.7)
Both eyes logMAR <1.0	3 (5.7)	2 (6.9)	NR	NR	NR	NR	NR	NR	NR	NR
One eye off-chart	11 (20.8)	3 (10.3)	Best VA: 18 (17.1)	Best VA: 17 (19.5)	NR	NR	NR	NR	NR	NR
Both eyes off-chart	25 (47.2)	13 (44.8)	NR	NR	NR	NR	12 (11.3)	7 (9.5)	19 (8.8)	19 (8.8)

	RHODOS		EAP		LEROS		CaRS I		CaRS II	
Both eyes on-chart	17 (32.1)	13 (44.8)	NR	NR	NR	NR	NR	NR	NR	NR
Patients with both eyes off-chart,* n (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Patients with discordant visual acuities,† n (%)	20 (37.7)	10 (34.5)	NR	NR	NR	NR	NR	NR	NR	NR
logMAR: mean ± SD,‡ (n)										
Best eye	1.61 ± 0.64 (53)	1.57 ± 0.61 (29)	1.16 ± 0.55	1.23 ± 0.52	1.15 ± 0.60	NR	0.75 ± 0.61	0.62 ± 0.61	0.94 ± 0.64 (438)	0.94 ± 0.64 (438)
Worst eye	1.89 ± 0.49 (53)	1.79 ± 0.44 (29)	NR	NR	NR	NR	NR	NR	NR	NR
Both eyes	1.75 ± 0.58 (106)	1.68 ± 0.54 (58)	NR	NR	1.26 ± 0.55	NR	1.03 ± 0.60	0.97 ± 0.63	NR	NR

*Off-chart defined as >logMAR 1.68 (patients unable to read any letter on the chart).

†Defined as patients with difference in logMAR>0.2 between both eyes

‡Applying logMAR 2.0 for counting fingers; logMAR 2.3 for hand motion; logMAR 2.6 for light perception

Abbreviations: EAP, Expanded Access Program; ITT, intent-to-treat; logMAR, logarithm of the minimum angle of resolution; NR – Not Reported; SD – Standard deviation;.

In terms of baseline characteristics, the EAG's clinical experts considered the population from studies included in the CS to be broadly representative of patients seen in clinical practice. However, they noted that patients across trials presented slightly older than the age at which patients tend to present in clinical practice, but the EAG does not consider this likely to impact the results. A further discrepancy was noted in the proportion of male participants in the LEROS trial, where it was [redacted] compared to the RHODOS, the EAP and CaRS-I and CaRS-II patients where the proportion of male patients better reflected UK clinical practice. However, the EAG notes that males still comprised the [redacted] of patients in the LEROS trial and that sex has not been highlighted as a prognostic factor for LHON by clinical experts or indicated in the submitted clinical evidence. Thus, the EAG has no concerns about any potential implication of this discrepancy on the results.

The EAG notes that the range in length of time since onset of vision loss in the RHODOS (2 to 62 months) and the LEROS trial (0.3 to 58.3 months) was wide, suggesting both trials included patients that were representative of both the incident and prevalent population of LHON. Given the range of time since onset of vision loss and the proportion of patients with onset of symptoms >1 year (44.4%) being close to 50%, the EAG notes the LEROS trial was representative of a mixture of patients in the acute, dynamic, and chronic phase of LHON. However, considering most patients in the RHODOS trial (~65%) had onset of symptoms >1 year and their baseline logMAR (>80% with logMAR≥1.0 in both eyes), the EAG considered the RHODOS patients to be more representative of patients in the chronic phase of the disease and less likely to be reflective of patients in the subacute or acute phase of the disease. Contrarily, based on their time since onset of vision loss, the EAG considers the EAP and CaRS patients (within 1 year for >90% of patients) to be representative of LHON patients in the acute and dynamic phase of the disease but not of the chronic phase. Thus, to include patients at an earlier stage of disease progression compared to RHODOS, LEROS and the prevalent population in England. Clinical experts advised the EAG that time since onset in the EAP and CaRS were more reflective of time to diagnosis seen in clinical practice compared to the RHODOS trial where participants' time since onset indicated they received idebenone much later than they would if it was to become available in clinical practice.

Considering the eligibility criteria for the EAP that was restricted to patients with onset of vision loss of less than 12 months (in the most recent eye) in addition to the time since onset of the included patients at baseline, the EAG considers the EAP and the CaRS study patients represent an incident population with LHON and has concerns over its applicability to the prevalent population with LHON

in England. Similarly, the eligibility criteria of the RHODOS trial limited the inclusion of participants to people with onset of vision loss ≤5 years. The EAG has concerns that the population for which data was available is of limited representativeness of the overall prevalent population in England, a considerable proportion of which will have LHON onset >5 years.

The EAG notes the distribution of mutations was largely in line with what is seen in clinical practice in England. However, it was noted that in the LEROS trial, the proportion of people with the m.11778G>A mutation, was [redacted] compared to the RHODOS trial, the EAP and CaRS. EAG clinical experts advised this mutation has the worse prognosis and a lower probability of spontaneous recovery compared to other mutations. Thus, the EAG has some concerns about the potential impact of a difference in the prevalence of mutations in the LEROS trial on the results. The EAG also noted that CaRS included a considerably larger proportion of patients with m.11778G>A mtDNA mutation compared to RHODOS, the EAP and the LEROS trial. EAG clinical experts have emphasised this mutation has a poorer prognosis, thus the EAG is concerned about the impact of this difference on the results and conclusions drawn about treatment with idebenone compared to the SoC using this retrospective review of medical records.

3.3 Critique of the clinical effectiveness analysis and interpretation

In Section B.2.6 of the company submission (CS), the company outlines results for primary and secondary outcomes of RHODOS, RHODOS-OFU and the Expanded Access Program (EAP). While the LEROS trial and matched natural history cohort from CaRS-I and CaRS-II were included in the submission, these are not focused on in the CS and were not included in the economic model due to "heterogeneity between patient populations" (see Section 4.2.4 on the EAGs critique). However, results from LEROS and its matched analysis were included in Appendix M to provide further evidence of the long-term efficacy of idebenone compared to SoC (see Section 3.4 on the EAG's critique of the matched-controlled analysis).

While the EAG agrees that the RHODOS trial is most relevant to the decision problem population given it was the only available RCT, the EAG raised concerns over the company's choice to present results for the mITT population over the ITT population, where possible for the primary efficacy analysis. The exclusion of one patient from the placebo group, that was considered a natural history confounder from the mITT, biases the results in favour of idebenone compared to the results from the ITT population. Therefore, the EAG requested that the company provide results from the ITT population. The request was fulfilled by the company and results are discussed below. While the

EAG considers that bias is likely to be associated with results of the mITT population from the RHODOS trial, the EAG considers it useful that these results are discussed alongside the ITT in the present report for comparative purposes.

All outcomes specified in the NICE final scope were presented in the CS. Changes in logMAR from the RHODOS trial, the EAP and CaRS-I and CaRS-II (natural history cohort) were used in the economic model by the company to inform transition probabilities. The company suggested that change in best VA was the most important outcome to consider, being the outcome that best reflects the impact of the disease on a patient and being the closest related to visual function in daily life. EAG clinical experts agreed change in best VA would be the most relevant outcome from a patients' perspective. Thus the EAG had no concerns over the choice of change in best VA over time as the outcome used to inform transition probabilities in the economic model. Specifically, data from the RHODOS trial informed transitions up to 6 months, while EAP data from patients in the efficacy population (N=87) informed transitions for over 6 months for up to 36 months. Although some patients in the EAP did provide follow-up visits post 36 months, with follow up ranging from 2.4 to 70.4 months, these occurred at variable time points and therefore could not be used to inform transition probabilities. Also, the number of patients on treatment >24 months was moderate (e.g. N=42; 48.3% at 24 months) in the efficacy population, and the number on treatment at 24 months was substantially reduced to nearly half by 36 months (N=23; 26%) with only 12 patients still receiving treatment at month 42.

3.3.1 Change in logMAR/ Change in best VA

3.3.1.1 RHODOS

In the RHODOS trial population, two analyses of changes in logMAR were presented:

- The best recovery of logMAR visual acuity in either right or left eye (primary efficacy endpoint);
- The change from baseline in patients' best VA.

As mentioned in Section 3.3, the EAG considers the change in patients' overall best VA to be the most clinically relevant endpoint, and therefore focuses on these analyses here. The results of the primary efficacy endpoint are summarised later in Table 16.

For the outcome of change in best VA, best VA at week 24 (best eye at Week 24) compared to best VA at baseline (best eye at baseline). Best recovery of logMAR VA in either right or left eye between baseline and Week 24 was reported for people with improving VA. In patients with neither eye improving in VA between baseline and Week 24, the change in VA representing the 'least worsening' was evaluated as 'best recovery'.

In the RHODOS ITT population, the difference between idebenone and SoC in the change in best VA from baseline to 24 weeks did not reach statistical significance. In people receiving idebenone, logMAR slightly improved with a change in logMAR of –0.035 (95% CI: –0.126 to 0.055), which equated to an improvement of only one letter on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. For people receiving placebo there was a worsening of logMAR +0.085; 95% CI: –0.032 to 0.203, which equated to worsening of 4 letters on the ETDRS chart. The between group difference was not statistically significant (logMAR –0.120, 95% CI: –0.255 to 0.014); equating to a 6-letter change (p = 0.078).

Best recovery of logMAR between baseline and 24 weeks for people receiving idebenone improved with a mean logMAR value of –0.135 (95% CI: –0.216 to –0.054). This equated to an improvement of 6 letters on the ETDRS chart. For people receiving placebo, the mean change from baseline also improved, with a logMAR value –0.071 (95% CI: –0.176 to 0.034), equating to an improvement of 3 letters on the ETDRS chart. The estimated mean difference between groups was not statistically significant (logMAR –0.064, 95% CI: –0.184 to 0.055); equating to a 3-letter change (p = 0.291).

Instead of the ITT population, the company presented the results of the RHODOS mITT population as the primary efficacy results in the CS. The RHODOS mITT population used the same population as the ITT but excluded one patient for VA data who had been randomised to placebo and was considered a natural history confounder due to an ongoing spontaneous recovery of vision at the time of randomisation. The EAG notes that the exclusion of one patient from the placebo group in the mITT analysis resulted in a considerable increase of the between group difference. However, when the analysis was based on the mITT population, the difference between treatment groups for all patients was still not statistically significant for the outcome of best recovery of logMAR VA (difference between groups –0.100, 95% CI –0.214 to –0.014; p = 0.0862), corresponding to a 5-letter difference on the ETDRS chart. Although, in the result for the change from baseline of best VA there was a statistically significant difference between groups in favour of idebenone (logMAR –0.160, 95% CI: –0.289 to –0.031; p = 0.015) that corresponded to an 8-letter difference on the ETDRS chart.

The EAG considers the results from the ITT population of RHODOS, which did not exclude any patients, are likely to be less biased compared to the mITT. The EAG notes that the patient excluded from the ITT population was identified as a natural history confounder due to on-going spontaneous recovery of vision at the time of randomisation to the study and their trajectory of VA being considered unusual compared to other patients, showing a marked improvement immediately prior to enrolment into the RHODOS trial. However, EAG clinical experts advised the EAG that spontaneous recovery of vision can reflect the natural progression of LHON in some patients. Thus, the EAG considers that the patient identified as a confounder should be included in the analysis.

The EAG also notes that this patient was excluded retrospectively and any criteria for exclusion from analysis had not been specified prospectively. Thus, the EAG considers the definition of the mITT population to be at high risk of bias.

3.3.1.2 RHODOS-OFU

The observational, single visit, follow-up study of RHODOS, RHODOS-OFU examined change in VA in 58 of the 85 patients originally included in the RHODOS trial for a median time of 30 months (range 20.9 to 42.5 months; 131 weeks). The mean change in best VA compared the results of the current VA with the observed VA at the original baseline and after 24 weeks of treatment in RHODOS. In patients in the placebo group, best VA at the RHODOS–OFU visit was slightly worse than at baseline (mean change in logMAR +0.039, corresponding to a worsening of 1 letter), whereas in the idebenone group best VA improved (mean change in logMAR –0.134, corresponding to an improvement of 6 letters). There was a benefit of treatment with idebenone that was maintained during the off–treatment period of the RHODOS–OFU follow-up but the difference between idebenone and placebo groups was not statistically significant (between group difference logMAR –0.173, 95% CI: –0.370 to 0.024; 8 letters; p = 0.0845). No statistical differences between groups were observed for baseline to week 24 of RHODOS (logMAR –0.175, 95% CI: –0.375 to 0.024; 8 letters; p=0.0844) or week 24 of RHODOS to the OFU visit (logMAR +0.002, 95% CI: –0.190 to 0.195; 0 letters; p=0.9819).

3.3.1.3 EAP and LEROS

The amount of data available at each timepoint from the key analysis set used from the EAP, LEROS and CaRS differed. Of the 87 patients with outcome data available at baseline in the EAP efficacy population, N=81 (93.1%) had data available >6 months, N=63 (72.4%) had data available>12 months

and 42 (48.3%) had data available >24 months. The EAG notes that the availability of outcome data over time from the LEROS ITT population was greater than the EAP. Of the 196 patients with outcome data available at baseline, N=171 (87.2%) had data available >6 months and N=151 (77%) had data available >12 months, and >24 months N=125 (63.7%) had data available, which indicated a significantly larger proportion compared to the EAP efficacy population at this time point.

In the EAP, there was a slight improvement in best VA from baseline to the last visit in the efficacy population (people who carried one of the three major LHON-causative mtDNA mutations with <12-month onset in the most recent eye), with logMAR decreasing from 1.23 (95% CI: –0.18 to 1.80) at baseline to 1.19 (95% CI: –0.16 to 1.80) at last visit.

In the LEROS trial, there was a slight improvement in best VA from baseline to 24 months in the ITT population with a mean (SD) change in logMAR of –0.09 (0.72) in people with disease onset in the second eye of ≤1 year and a mean (SD) change in logMAR of –0.19 (0.31) in people with disease onset in the second eye of >1 year.

3.3.1.4 CaRS-I and CaRS-II

The number of patients with outcome data available overtime from the CaRS-I natural history outcomes population was unclear, while the availability of outcome data from CaRS-II natural history population reduced substantially overtime, with N=203 (92.7%) of the total 219 people with data >6 months, N=58 (26.5%) with outcome data available >12 months and N=26 (11.9%) with outcome data available >24 months.

[redacted]

[redacted]

Data is mean (and 95% CI) of VA data from the Natural History Population over time since Onset of symptoms. Note: logMAR VA means and CIs calculated using logMAR 1.7 for all off-chart VA categories.

The distribution of all eyes of patients within the Natural History Outcomes Population between VA categories of logMAR <1.0, logMAR 1.0-1.68 or logMAR >1.68 ('off-chart' VA) at presentation, nadir and outcome assessment is presented in Figure 4 below.

Figure 4. Analysis by VA Category for Eyes at Presentation, Nadir and Outcome in the Natural History Outcomes population (reproduced from Case Record Survey CSR)

[redacted]

[redacted]

[redacted]

In CaRS-II, best VA was assessed during the periods of time indicated in the Table 15 below.

[redacted]

Table 15. Best VA at follow-up (reproduced from Table 11.3.1 in CaRS-II CSR)

	≤ 1 year (N=203)	1 to 2 years (N=58)	2 to 3 years (N=26)	3 to 4 years (N=25)	4 to 5 years (N=18)	> 5 years (N=37)
Best VA within 1 year follow-up (logMAR)						
Mean ± SD	[redacted]					
Median (Q1 – Q3)	[redacted]					
Min – Max	[redacted]					
Best VA within 1 year follow-up (blindness category)						
off-chart	[redacted]					
1.0 to 1.68 logMAR	[redacted]					
< 1.0 logMAR	[redacted]					
Difference in Best logMAR from visit and Baseline						
Mean ± SD	[redacted]					
Median (Q1 – Q3)	[redacted]					
Min – Max	[redacted]					

The data used from the CaRS studies are discussed in greater detail in Section 3.4.

3.3.2 Other Outcomes

The EAG notes that to evaluate the effectiveness of idebenone to prevent further vision loss (stabilisation) and recover lost vision (recovery), the company defined a clinically relevant benefit (CRB) to include clinically relevant recovery (CRR) or clinically relevant stabilisation (CRS) of visual acuity (VA). Across trials, CRR is defined as improvement of at least logMAR 0.2 (equal to two lines of readable letters on a logMAR chart) for patients with "on-chart" VA at baseline, or an improvement from "off-chart" VA to at least logMAR 1.6 (equal to one line on-chart) for patients with off-chart VA at baseline.

In the RHODOS trial, a higher proportion of patients in the idebenone group (ITT: 30.2%; n=16) than in the placebo group (ITT: 10.3%, n=3) showed CRR from baseline, but the difference between groups was not statistically significant (p=0.056).

In the EAP, of the 87 patients included in the efficacy population, 40 patients (46.0%) (by eyes, 67/173; 38.7%) had CRR from nadir to the last observation visit. The average magnitude of recovery, defined based on a patients' best recovering eye, corresponded to 22 letters (0.45 logMAR) on the ETDRS chart at the initial observation of CRR and increased with prolonged treatment to 36 letters (0.72 logMAR) at the last observation.

In LEROS, the proportion of eyes that achieved CRR of VA from baseline at 12 months was reported for patients who started treatment with idebenone ≤1 year after the onset of symptoms compared to eyes in the matching external natural history control group.

[redacted]

[redacted].

[redacted]

[redacted].

The EAG has concerns about CRR relating to the extent to which it reflects the effect of treatment with idebenone. The EAG notes the considerable proportion with CRR from nadir in CaRS-I was achieved without receiving treatment and could therefore have been a result of spontaneous recovery. Thus, the EAG has concerns about the extent to which CRR constitutes a good indication of treatment effectiveness of idebenone. See Section 4.2.4 for further discussion of CRR.

3.3.3 Comparison across studies

Outcomes demonstrating change in logMAR (change in best VA, best recovery of logMAR VA in either right or left eye, CRR) from the RHODOS trial, EAP, and LEROS discussed previously are presented in Table 16 below. Where change from baseline scores are reported in the studies, a positive logMAR value (showing an increasing logMAR) indicated worsening and negative logMAR value (showing a decreasing logMAR) indicated improvement.[41]

Table 16. Visual acuity outcome data (adapted from Table 10 from company's initial clarification response)

Outcome (95% CI) [equivalent EDTRS letters]		RHODOS		EAP		LEROS	
		Idebenone	Placebo	LHON population	Efficacy population	ITT	NH matched comparator
	N	53	29	105	87	196	106
	Timepoint	Week 24		Final analysis time-point		Month 24	
Best logMAR at baseline, mean (95% CI)	Baseline	1.61±0.64	1.57±0.61	1.16 (–0.18 to 1.80)	1.23±0.52 (–0.18 to 1.80)	[redacted]	—
Best logMAR at final visit	Final analysis time-point	—	—	1.09±0.66 (–0.18 to 1.80)	1.19±0.63 (–0.16 to 1.80)	[redacted]	—
Change in best VA (from baseline)	Final analysis time-point	–0.035 (–0.126 to 0.055) [+1 letter]	0.085 (–0.032 to 0.203) [–4 letters]	—	—	N= 70 2nd eye onset ≤1 year: –0.09 min –1.78, max 1.84 N=55 2nd eye onset >1 year: –0.19 min –1.24, max 0.12	Data only reported for individual eyes
Best recovery of logMAR visual acuity in either right or left eye (from baseline)	Final analysis time-point	–0.135 (–0.216 to –0.054)	–0.071 (–0.176 to 0.034)	Not an outcome measure	Not an outcome measure	Not an outcome measure	Not an outcome measure

		[+6 letters]	[+3 letters]				
CRR (from baseline)	Final analysis time-point	Patients:16, 30.2%	Patients: 3, 10.3%	Patients: 42, 40.00%	Patients: 31, 35.63%	Eye onset ≤ 1 year: N=44, 40.4% Eye onset>1 year N=33 (32.4%)	—
CRR (from nadir)	Final analysis time-point	Not an outcome measure	Not an outcome measure	53, 50.5%	40, 46.0%	Eye onset ≤ 1 year: N=53, 48.6% Eye onset >1 years: N=37, 36.3%	—

Abbreviations: CRR, clinically relevant recovery; ETDRS, Early Treatment Diabetic Retinopathy Study; ITT, intent-to-treat; logMAR, logarithm of the minimum angle of resolution; NH, natural history; VA, visual acuity

3.3.4 Subgroup analyses

Various subgroup analyses of data had been carried out to provide additional information on the effect of idebenone on VA: the subgroup of patients with logMAR <1 at baseline compared to patients with logMAR ≥1 from the RHODOS trial; patients with disease duration ≥1 year and disease duration <1 year; patients with different mtDNA mutations; and patients with discordant VA at baseline. These were presented in Sections B.2.6 and B.2.7 in the CS. Overall, the EAG notes that due to the rarity of LHON and the limited number of patients for each subgroup, it is difficult to draw robust conclusions about the effect of idebenone from any of the presented analyses.

In addition, the EAG notes that disease duration (≥1 year vs <1 year) is a potentially problematic dichotomisation as according to input from EAG clinical experts, it is noted that the majority of patients may have already hit nadir within the first year of onset and a 'nadir' health state may also be a prognostic factor impacting disease severity and confounding with the treatment effect.

3.3.5 Quality of life

Health-related quality of life (HRQoL) data were available from the RHODOS trial and RHODOS-OFU. These were obtained using the Visual Function (VF)-14 tool, the Clinician's Global Impression of Change (CGIC) score and the visual analogue scale (VAS). As discussed further in Section 4.2.6, HRQoL data derived from the RHODOS and RHODOS-OFU trial were not used in the economic model.

Over the 24-week follow-up of RHODOS, only small changes were observed in VF-14 and the difference between treatment groups in change of VF-14 score was not statistically significant (estimated mean treatment difference – 1.37; 95% CI: –6.25 to 3.51; p = 0.577). VF-14 data were available from 57 patients taking part in the RHODOS-OFU. The overall changes between VF-14 score recorded during RHODOS and RHODOS-OFU were small and differences between idebenone and placebo groups were not statistically significant. There was a small worsening in HRQoL in the idebenone group (–1.7%), whereas there was a small improvement in the placebo group (2.4%) for the entire period between RHODOS baseline to RHODOS-OFU (the between group difference was not statistically significant, p = 0.205).

Although statistical analysis on CGIC scores was not reported, at week 24 of RHODOS, 12 patients (22.6%) in the idebenone group and 7 patients (24.1%) in the placebo group from the ITT population had an improvement in overall CGIC scores. A total of 43 patients (81.1%) in the idebenone group and 24 patients (82.8%) in the placebo group reported experiencing less fatigue or no change in fatigue levels. At week 24, patients in both treatment groups reported minimally elevated energy levels assessed by the VAS (0.37 mm for idebenone and 2.17 mm for placebo) with no statistically significant difference between the treatment groups (estimated mean treatment difference –1.80; 95% CI: –11.37 to 7.77; p = 0.709).

The EAG and its clinical experts partially agree with the company's conclusion that the duration of the RHODOS trial (24 weeks) may not have been long enough to show the treatment benefit of idebenone. In addition, the EAG considers it likely that a larger sample size with a longer follow-up would be required to allow for a minimum clinically important change in VA to be detected.

3.3.6 Safety

Adverse event (AE) data are available from RHODOS, LEROS, the EAP and PAROS. Few safety data were available for placebo or untreated patients, as RHODOS was the only RCT, and safety data were not collected in the CaRS natural history studies.

The frequency of AEs reported in RHODOS and LEROS are presented in Table 17. In RHODOS, the proportion of patients experiencing AEs was similar between the idebenone and placebo groups. A slightly higher proportion of participants in the idebenone arm reported nasopharyngitis (idebenone: 25.5%; placebo: 16.7%); cough (idebenone: 10.9%; placebo: 0%); dizziness (idebenone: 5.5%; placebo: 0%); and left ventricular hypertrophy (idebenone: 7.3%; placebo: 0%). The number of idebenone treated individuals experiencing AEs in LEROS was similar in LEROS compared to RHODOS, with a small but expected increase in the number of investigations in LEROS, given the longer duration of follow up.

Table 17. Number of people experiencing at least one adverse event in RHODOS and LEROS

	RHODOS			LEROS
N (%) subjects	Idebenone 900 mg/day (N=55)	Placebo (N=30)	All Subjects (N=85)	Idebenone 900 mg/day (Safety Population) (N=198)
Timepoint	Through Visit 6 (28 to 35 days after drug discontinuation)			Through study completion (average of 24 months)
AE definition	Treatment-emergent AEs by Preferred Term reported by at least 2 patients in either arm, MedDRA 13.0, N (%)			Treatment-emergent AEs by Preferred Term reported by ≥5% patients in LEROS, or by at least 2 patients in a RHODOS arm, MedDRA 24.0, N (%)
N (%) with at least 1 severe adverse event	2 (3.6)	0	2 (2.4)	13 (6.6)
Cardiac disorders				
Left ventricular hypertrophy	4 (7.3)	0	4 (4.7)	NR
Gastrointestinal disorders				
Upper abdominal pain	3 (5.5)	3 (10.0)	6 (7.1)	13 (6.6)
Constipation	2 (3.6)	3 (10.0)	5 (5.9)	2 (1.0)
Diarrhoea	5 (9.1)	3 (10.0)	8 (9.4)	19 (9.6)
Flatulence	0	2 (6.7)	2 (2.4)	NR
Vomiting	4 (7.3)	2 (6.7)	6 (7.1)	6 (3.0)
Nausea	NR	NR	NR	15 (7.6)
Infections and infestations				
Gastroenteritis	1 (1.8)	2 (6.7)	3 (3.5)	4 (2.0)
Influenza	6 (10.9)	3 (10.0)	9 (10.6)	8 (4.0)

Nasopharyngitis	14 (25.5)	5 (16.7)	19 (22.4)	33 (16.7)
Sinusitis	1 (1.8)	2 (6.7)	3 (3.5)	7 (3.5)
Investigations				
Alanine aminotransferase increased	1 (1.8)	3 (10.0)	4 (4.7)	17 (8.6)
Blood cholesterol increased	0	2 (6.7)	2 (2.4)	4 (2.0)
Blood creatine phosphokinase increased	1 (1.8)	2 (6.7)	3 (3.5)	15 (7.6)
Blood triglycerides increased	6 (10.9)	3 (10.0)	9 (10.6)	5 (2.5)
Gamma-glutamyl transferase increased	0	5 (16.7)	5 (5.9)	10 (5.1)
Aspartate aminotransferase increased	NR	NR	NR	14 (7.1)
Musculoskeletal and connective tissue disorders				
Arthralgia	0	2 (6.7)	2 (2.4)	3 (1.5)
Back pain	4 (7.3)	2 (6.7)	6 (7.1)	9 (4.5)
Nervous system disorders				
Dizziness	3 (5.5)	0	3 (3.5)	5 (2.5)
Headache	13 (23.6)	6 (20.0)	19 (22.4)	37 (18.7)
Respiratory, thoracic, and mediastinal disorders				
Cough	6 (10.9)	0	6 (7.1)	12 (6.1)
Oropharyngeal pain	5 (9.1)	3 (10.0)	8 (9.4)	14 (7.1)
Skin and subcutaneous tissue disorders				
Pruritus generalised	1 (1.8)	2 (6.7)	3 (3.5)	NR
Rash	2 (3.6)	2 (6.7)	4 (4.7)	6 (3.0)

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

Sources: CS Table 22; LEROS clincialtrials.gov record[39]

Limited safety data were presented from the RHODOS-OFU single visit: the CS quoted pages 69 and 70 of the EMA European Public Assessment Report of idebenone, which stated that: "*Of the 60 patients included in the Safety Population of RODOS-OFU, there was one SAE of hypertensive emergency experienced on the day of the RHODOS-OFU visit, which was over 3 years after completing. The investigator considered this event not related to study drug received in RHODOS. No other relevant safety findings were derived from RHODOS-OFU.*"[24]

In PAROS, the prospective non-interventional post-authorisation safety study of idebenone, the following primary endpoints were measured:

- Frequency of AEs of special interest
  ([redacted]
- Frequency and nature of AEs and serious AEs;
- Frequency and nature of adverse drug reactions and serious adverse drug reactions.

The frequency of AEs of special interest and the frequency of AEs and serious AEs observed in PAROS were reported in Table 11 and Table 12 of the company response to clarification, respectively. These results are in-line with the safety findings of RHODOS and LEROS.

Safety data were also available from the EAP safety population (N=111).
[redacted]The EAG considers these data to be in line with RHODOS and LEROS.

AEs were not included in the economic model given that most AEs experienced were considered mild in all safety studies conducted.

3.3.6.1 EAG summary of safety data

The EAG notes the overall incidence of AEs across the idebenone clinical trial programme and real-world evidence studies was low, and few AEs were classed as severe. For the only data set in which a

placebo cohort were available, RHODOS, the proportion of patients experiencing AEs was similar in the idebenone arm compared to the placebo arm, with the potential exceptions of nasopharyngitis (idebenone: 25.5%; placebo: 16.7%); cough (idebenone: 10.9%; placebo: 0%); and dizziness (idebenone: 5.5%; placebo: 0%). These AEs were not classed as severe, and the EAG considers that even if the increases observed in RHODOS were observed in clinical practice, they would be unlikely to have a meaningful impact on the cost-effectiveness of idebenone.

The EAG notes that there is an absence of long-term placebo-controlled data on the safety of idebenone for treating LHON, but the EAG was reassured that the proportion of patients experiencing AEs did not meaningfully increase in the longer term LEROS clinical trial and the EAP and PAROS observational studies.

3.3.6.2 Left ventricular hypertrophy

In RHODOS, four (7.3%) idebenone patients compared to 0 (0%) placebo patients experienced left ventricular hypertrophy. The EAG notes this was explored by the EMA in the European Public Assessment Report, which considered that:[24]

- In RHODOS, only one case of left ventricular hypertrophy was considered related to idebenone treatment;
- All left ventricular hypertrophy events were non-serious and were reported by the same investigational site;
- The diagnoses was not supported by clinical or ultrasound evidence;
- The incidence of ECG findings suggestive of left ventricular hypertrophy developing after initiation of the study treatment was lower in the idebenone group (7.27%) than in the placebo group (13.33%);
- When considering data also from research in patients treated with idebenone for Friedreich's ataxia, there was no demonstrated signal of any ECG abnormality in heart rate for individuals treated with idebenone.

The EAG further notes that left ventricular hypertrophy was not reported as an observed AE in LEROS, PAROS, or the EAP. The EAG, therefore, considers it unlikely that idebenone is related with the development of left ventricular hypertrophy in people with LHON.

3.3.7 Discussion of clinical effectiveness evidence

As discussed further in Section 4.2.4, the EAG has concerns over the preference of the EAP over the LEROS trial data to inform the clinical and cost-effectiveness of idebenone beyond 6 months (6 to 36 months).

The company argues that the EAP should be preferred over LEROS due to heterogeneity in the proportion of males between the LEROS trial [redacted] and the RHODOS trial (85.9%) that was used to inform the clinical and cost-effectiveness of idebenone for the first 6 months of treatment. The EAG notes that although the proportion of males was more comparable between the RHODOS trial and the EAP (82%), males in the LEROS trial still constituted [redacted] patients. Taking this into consideration in addition to that it is unclear if sex is a prognostic factor impacting disease severity,[42] and that there was no substantial difference in outcome data between the LEROS trial, the RHODOS trial and EAP, the EAG has concerns over the rationale for the company's preference for the EAP over LEROS.

The EAG notes that the genetic mutation distribution of the RHODOS trial population consisting of people carrying three mutations (m.11778G>A [67.3%], m.14484T>C [20%], m.3460G>A [12.7%]) was more aligned with the EAP population compared to LEROS population, which consisted of patients from a wider range of LHON mutations (m.11778G>A [redacted] m.14484T>C [redacted] m.3460G>A [redacted] Negative [redacted] Other [redacted]) than the EAP study (m.11778G>A [62.1%], m.14484T>C [18.4%] m.3460G>A [19.5%]).

In addition, the EAG notes that the EAP provides more longer-term data for up to 36 months compared to the LEROS trial with data for up to 24 months, but that these data are limited with LEROS (N=199) providing data for a larger data set than the EAP (N=87), potentially making it a better choice to inform the long-term effectiveness of idebenone. The EAG also notes that time since onset in the RHODOS and LEROS trial is comparable (≤5 years) but differs in the EAP including patients with onset of vision loss in the second eye less than 12 months. EAG clinical experts agreed that time since onset is an important prognostic factor for that can impact treatment effectiveness. The EAG's concerns over the difference in time since onset between the data sets also include the greater chance of spontaneous recovery present during the first year of onset as highlighted by the clinical experts, which could introduce further bias in the interpretation of the results.

3.4 Critique of the indirect comparison treatment comparison

3.4.1 Trials informing the indirect treatment comparison

A direct head-to-head comparison of idebenone and SoC for 6 months of treatment is available from the RHODOS trial. After this, no RCT data comparing long-term treatment with idebenone and SoC are available. In the company base case, the long-term treatment effects of idebenone and SoC are modelled using two unmatched populations: the EAP population for idebenone and the CaRS-I and CaRS-II natural history (NH) populations for SoC. Such a comparison is at high risk of bias due to imbalances in prognostic factors between patients in the EAP and the CaRS studies, for example, differences in the prevalence of each major three mutation type (Section 3.2.5).

The EAG considers that matching the idebenone and SoC cohorts would provide a less biased method to model the long-term treatment effect of idebenone compared to SoC, but notes no matched control analyses were provided in the original CS. Following a request by the EAG at the clarification stage, the company provided a propensity-score matching (PSM) analysis of changes in patient's best visual acuity between LEROS and CaRS-I and CaRS-II at Month 24.

3.4.2 Statistical methods

The company's PSM analyses compared LEROS ITT patients at 24 months with SoC CaRS-I and CaRS-II SoC patients. The following prognostic factors were included in the calculation of the propensity score:

- Sex;
- Age at first symptom onset;
- Genotype;
- Months since the most recent symptom onset;
- Months since first symptom onset;
- Number of symptomatic eyes at baseline;
- Baseline logMAR for the left eye; and
- Baseline logMAR for the right eye.

Rather than matching patients at baseline and then including all subsequent follow-up visits in the analysis, the PSM analyses were conducted using a single baseline and 24-month visit window only. The following process was conducted to match patients:

- A subset of NH patients from CaRS-I and CaRS-II were selected who had a pair visits 24 months apart (within a window of 3 months) – matching the "baseline" and 24-month visit in LEROS. This created a total sample of 84 patients with 270 potential visit pairs 24 months apart for matching;
- Through PSM, 68 of the 84 available NH patients to be matched to 68 of 125 LEROS ITT patients.

PSM was conducted using a nearest neighbour approach with a calliper width of 0.2 time the standard deviation of the logit of the PS. The PSM analyses were implemented in SAS 9.4.

The baseline characteristics of the matched patients are displayed in Table 18.

Table 18. Baseline characteristics of idebenone treated patients (LEROS ITT) matched to SoC treated patients (CaRS-I and CaRS-II).

Baseline Characteristic	Matched SoC (CaRS) N = 68	Matched Idebenone (LEROS) N = 68
Gender		
Female	11 (16.2%)	15 (22.1%)
Male	57 (83.8%)	53 (77.9%)
Genotype		
m.11778G>A	40 (58.8%)	[redacted]
m.3460G>A	14 (20.6%)	[redacted]
m.14484T>C	9 (13.2%)	[redacted]
Other	5 (7.4%)	[redacted]
Age at 1st symptom onset		
Mean ± SD	26.2±15.3	29.7±13.6
Median (Q1-Q3)	21.0 (15.5 to 36.5)	26.7 (19.1 to 39.1)
Eyes affected at baseline		
1	0 (0.0%)	4 (5.9%)
2	68 (100.0%)	64 (94.1%)
Months since 1st symptoms onset		
Mean ± SD	18.2±22.3	18.1±16.6
Median (Q1-Q3)	13.2 (5.5 to 21.4)	11.8 (6.1 to 23.8)
Min - Max	0.0 to 134.1	0.3 to 58.3
Months since most recent symptoms onset		
Mean ± SD	17.1±21.9	16.3±16.5
Median (Q1-Q3)	11.3 (4.1 to 20.4)	9.4 (4.6 to 23.5)

Min - Max	0.0 to 134.1	0.0 to 57.6
Baseline best VA logMAR		
Mean ± SD	1.19±0.53	1.16±0.60
Median (Q1-Q3)	1.30 (0.90 to 1.80)	1.31 (0.69 to 1.65)
Min - Max	–0.20 to 1.80	–0.12 to 1.80
Baseline best VA		
Light Perception	0 (0.00%)	1 (1.47%)
Hand Motion	4 (5.88%)	6 (8.82%)
Counting Fingers	13 (19.12%)	9 (13.24%)
logMAR >= 1.3 and < 1.7	20 (29.41%)	20 (29.41%)
logMAR >= 1.0 and < 1.3	13 (19.12%)	9 (13.24%)
logMAR >= 0.6 and < 1.0	10 (14.71%)	9 (13.24%)
logMAR >= 0.3 and < 0.6	4 (5.88%)	4 (5.88%)
logMAR < 0.3	4 (5.88%)	10 (14.71%)

Abbreviations: ITT, intention to treat; logMAR, Logarithm of the minimum angle of resolution; NH, Natural history; Q, Quartile; SD, Standard deviation; SoC, standard of care; VA, Visual acuity

Source: Company response to clarification Table 5.

The EAG considers the baseline characteristics of matched cohorts to be reasonably balanced, and considerably less imbalanced than the original unmatched samples (Section 3.2.5). The EAG notes two small remaining imbalances in patient baseline characteristics:

- The age of first symptom onset is younger for the SoC cohort than the idebenone cohort, which is likely associated with a greater probability of spontaneous recovery in the SoC cohort;
- The prevalence of the milder T14484C genotypes is slightly higher in the idebenone cohort than the SoC cohort, which is likely associated with a greater probability of spontaneous recovery in the idebenone cohort.

The company implemented two analysis of covariance (ANCOVA) models to perform a comparison of change in best logMAR VA between matched idebenone and SoC patients. The first model included all patients and had treatment as a sole predictor. The second model included treatment, genotype and a treatment-by-genotype interaction as predictors, and limited the analysis population to patients with one of the three major genotypes.

3.4.3 LEROS ITT vs CaRS-I and CaRS-II ITC results at 24 months

Full results of the PSM comparison between LEROS and the CaRS studies are presented in the company response to clarification question A2. Here, the EAG focuses on the most relevant outcome for the economic model, change in best logMAR VA.

The results of the change in best logMAR VA model with treatment as a single predictor are presented in Table 19. There was no statistically significant difference in the change in best logMAR VA at 24 months between idebenone, –0.13 (95% CI: –0.27 to 0.02), and matched NH controls, –0.11 (95% CI: –0.26 to 0.04), with similar point estimates and confidence intervals between the groups.

Table 19. PSM analysis of change in best VA at 24 months between idebenone treated patients (LEROS ITT) matched to SoC treated patients (CaRS-I and CaRS-II). Adapted from company response to clarification Table 8.

Treatment	Change in best VA at 24 months, logMAR LS-Means (95% CI)	LS-Means p-value
Idebenone	–0.13 (–0.27 to 0.02)	0.097
SoC	–0.11 (–0.26 to 0.04)	0.152
Difference	–0.02 (–0.23 to 0.19)	0.871

ANCOVA with treatment as covariate

Abbreviations: CI, Confidence interval; ITT, intention to treat; LS, Least squares; logMAR, Logarithm of the minimum angle of resolution; SoC, Standard of care; VA, Visual acuity

Source: Company response to clarification Table 8

Table 20 presents the results of the alternative change in best logMAR VA model with treatment, genotype and a treatment-by-genotype interaction as predictors, and the limited analysis population to patients with one of the three major genotypes. Conditional on genotype and the interaction between genotype and treatment, there was no statistically significant difference in the change in best logMAR VA at 24 months between idebenone, –0.14 (95% CI: –0.29 to 0.02), and matched NH controls, –0.24 (95% CI: –0.41 to –0.07), although the point estimate numerically favoured SoC.

Table 20. PSM analysis of change in best VA at 24 months between idebenone treated patients (LEROS ITT, major 3 genotypes only) matched to SoC treated patients (CaRS-I and CaRS-II). Adapted from company response to clarification Table 9.

Treatment	Major 3 genotypes	Change in best VA at 24 months, logMAR LS-Means	LS-Means p-value
Idebenone	_	–0.14 (–0.29 to 0.02)	0.085
NH	_	–0.24 (–0.41 to –0.07)	0.007

Difference	_	0.10 (–0.13 to 0.34)	0.381
Idebenone	G11778A	–0.07 (–0.25 to 0.11)	0.436
Idebenone	G3460A	0.17 (–0.13 to 0.46)	0.263
Idebenone	T14484C	–0.50 (–0.82 to –0.19)	0.002
NH	G11778A	0.07 (–0.11 to 0.25)	0.471
NH	G3460A	–0.30 (–0.61 to 0.00)	0.049
NH	T14484C	–0.48 (–0.86 to –0.10)	0.013
Difference	G11778A	–0.14 (–0.39 to 0.12)	0.289
Difference	G3460A	0.47 (0.05 to 0.89)	0.029
Difference	T14484C	–0.02 (–0.52 to 0.47)	0.923

ANCOVA with treatment and mutation as covariates type 3 test of fixed effects p-values:

- Treatment p = 0.381
- Genotype p = 0.028
- Treatment*Genotype p = 0.534

Abbreviations: CI, Confidence interval; ITT, intent-to-treat; LS, Least squares; logMAR, Logarithm of the minimum angle of resolution; NH, Natural history; VA, Visual acuity

Source: Company response to clarification Table 9

An analysis of the subgroup of LEROS ITT patients matched to CaRS patients in the subacute phase of LHON, defined as only those visits where the most recent symptom onset occurred within the last year, was also presented in the company response to clarification question A2. The EAG notes the result of this smaller sample analysis was in-line with the full population: no statistically significant differences between idebenone and SoC in the change in best logMAR VA at Month 24.

3.4.4 EAG critique

The results of these PSM analyses do not provide strong evidence of a clinically meaningful long-term treatment benefit of idebenone over SoC for the treatment of LHON, and the company did not provide a detailed interpretation of the results of the PSM analyses. The EAG notes that:

- The PSM analysis is currently the only available matched cohort analysis of the effects of long-term idebenone treatment compared to SoC;
- These data do not provide strong evidence of a clinically meaningful long-term treatment benefit of idebenone over SoC for the treatment of LHON;
- There are several limitations to the PSM analysis – which was conducted over a short time frame during the clarification stage – but the EAG considers the analysis to be reasonably unbiased;

- The face validity of the point estimates of a negligible (Table 19) or negative (Table 20) long-term treatment benefit of idebenone over SoC may be low, and suggests this PSM analysis underestimates the long-term treatment effect of idebenone, despite being considered by the EAG as the most appropriate analysis of the comparative effectiveness of long-term idebenone treatment compared to SoC that is currently available.

The EAG completed a quality of effectiveness estimates from non-randomised studies (QuEENS) checklist for the PSM analyses, which is presented in Appendix 8.1.[43] The EAG notes that several areas highlighted as lower quality for the PSM analyses, such as comparing different analysis methods, were likely infeasible during the 4-week window the analyses were conducted. The EAG is most concerned that only a limited amount of CaRS follow-up data were included in the analyses by choosing to only analyse a single visit pair, rather than all available data, for SoC patients. The EAG also notes that this prevented the data from the matched-control analysis being used in the economic model, as the company explained in response to further clarification:

> *"The company [performed] the matching algorithm for individual patients as per the request for A2, however the per cycle transition counts cannot be derived as the same patient will not be followed over the trial duration and therefore, their movement across health states cannot be accurately captured (matching algorithm was performed de novo at each time point, implying that different patient subsets from the CaRS trial were included at each timepoint)."*

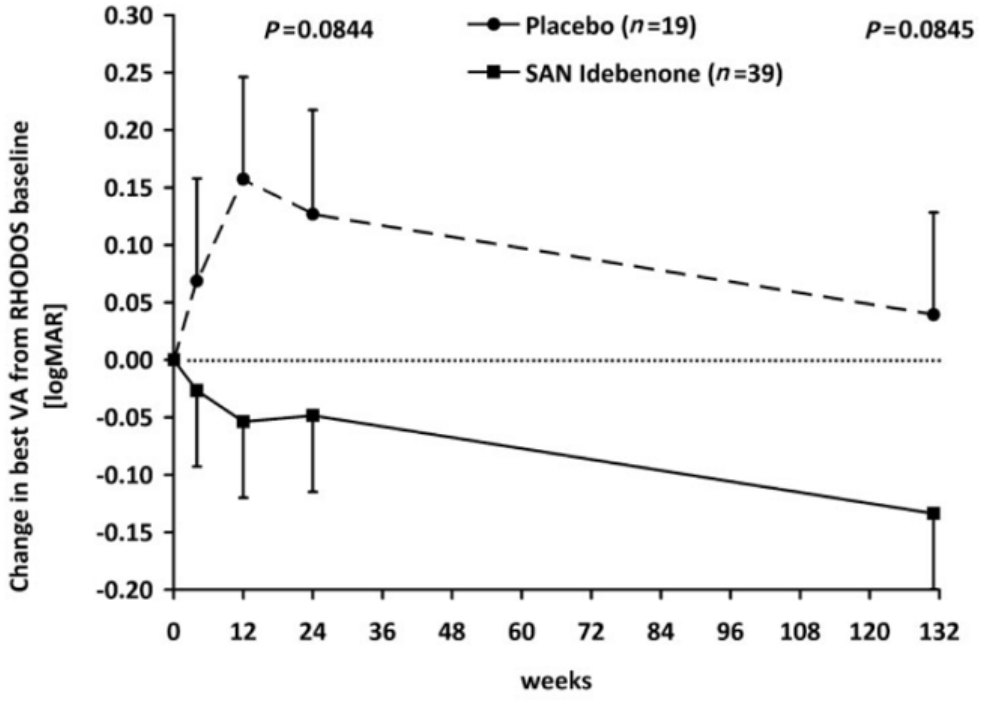
The EAG's preferred approach would have been to match patients between LEROS and CaRS at baseline and use all available follow-up data in analysis. The EAG considers that, since the median time between visits was 11.7 months in CaRS, restricting the analysis set to visit pairs 24 months apart likely does not make best use of the available data. Nevertheless, at the current time, the PSM analysis presented in the company's response to clarification is the only available long-term matched-control comparison of changes in patients' best logMAR VA over time between idebenone and SoC, which does not provide strong evidence of a clinically meaningful long-term treatment benefit of idebenone over SoC for the treatment of LHON.

The EAG notes that a single long-term follow-up datapoint is available from N=58 participants from the RHODOS trial in the OFU visit, presented in Section 3.3.1.2. This provides data on the long-term outcomes of people previously treated with idebenone (for 6 months) compared to SoC for a

duration of 6 months only, up to Week 132. These data are reproduced in Figure 5. Through Week 132, the estimated difference in best VA between patients treated with 6 months of idebenone compared to SoC was −0.173 (95% CI: −0.370 to 0.024), equivalent to 8 ETDRS letters. This difference was not statistically significant (p = 0.0845). The EAG notes that:

- The RHODOS RCT and OFU data are more consistent with a positive long-term treatment effect of idebenone compared to SoC compared to the PSM analyses;
- The RHODOS OFU visit data may slightly overestimate the long-term treatment effect of 6-months of idebenone treatment compared to SoC due to a selection bias at patient entry favouring idebenone:
    - In the full RHODOS RCT ITT population, the between group difference (idebenone – SoC) at Week 24 was −0.120 (95% CI: −0.255 to 0.014), equivalent to 6 ETDRS letters;
    - In the subgroup of patients comprising the RHODOS OFU population, the between group difference (idebenone – SoC) at Week 24 was −0.175 (95% CI: −0.375 to 0.024), equivalent to 8 ETDRS letters. That is, the patient population entering the RHODOS OFU visit had a larger treatment effect at Week 24 than the ITT population from which it was sampled.

Figure 5. Change in visual acuity over time for the best visual acuity (logMAR), RHODOS OFU cohort (Reproduced from CS Figure 15)



Data are estimated means ± SEM from MMRM, based on the change from baseline (in weeks) and plotted for the two treatment groups as defined in the RHODOS study. No treatment was given between Week 24 and Week 131. Worsening/improvement of visual acuity is indicated as positive/negative values in change of logMAR. A difference of logMAR 0.1 corresponds to five letters or one line on the Early Treatment Diabetic Retinopathy Study chart. The P-values are given for the difference between treatment groups.
Source: Reproduced from CS Figure 15. Klopstock T et al, 2013 (19)
Abbreviations: logMAR, Logarithm of the minimum angle of resolution; MMRM, Mixed-model of repeated measures; SEM, Standard error of the mean; VA, Visual acuity

Hence, at the time of the EAG report, the EAG notes three available approaches to modelling the long-term treatment effect of idebenone vs SoC:

- A PSM analysis of LEROS and the CaRS studies that does not provide strong evidence of a clinically meaningful long-term treatment benefit of idebenone over SoC for the treatment of LHON, but is the only source of matched-control data for patients treated with idebenone for > 6 months;
- The RHODOS OFU visit, providing data on the Week 132 outcomes of patients previously treated with idebenone or SoC for 6 months, followed by SoC for both treatment arms up to Week 132; and
- An unmatched comparison of the EAP or LEROS and the CaRS studies, employed in the current company base case, that is at high risk of bias due it being a naïve comparison with imbalances in prognostic factors between patient cohorts.

The EAG notes that a matched-control analysis of individual eyes between LEROS and CaRS-I and CaRS-II patients was presented in the LEROS CSR, and summarised in the CS Appendix M. As highlighted in Clarification Question A1, the EAG did not consider this analysis appropriate to inform a cost-effectiveness analysis of idebenone as the analysis focused on outcomes within individual eyes, rather than at the more relevant level of the individual patient. Moreover, the EAG noted in Clarification Question A1 (f) that the “matching” procedure only matched CaRS patients’ visit pairs times to the average time since onset of symptoms at baseline calculated for LEROS. The EAG does not consider that this procedure matches patients on key prognostic factors, such as LHON genotype baseline VA, and is therefore at high risk of bias. The EAG notes that the PSM analyses provided at the individual patient level follows a similar approach to the “by eye” analysis originally presented, but also matches patients based on these key prognostic factors.

3.5 Conclusions of the clinical effectiveness section

The EAG concludes that although the RHODOS trial provided randomised controlled evidence on the efficacy of idebenone compared to standard of care (SoC) for up to 6 months (24 weeks), evidence on the long-term effects of idebenone has been limited.

No RCT data comparing long-term treatment with idebenone and SoC are available as evidence has been limited to observational data with inherent limitations such as the open-label and uncontrolled nature of the data collection in the EAP, the retrospective analysis of patient records in the CaRS studies and the considerable loss of data during follow-up across sources of data. Long-term effectiveness beyond 6 months was modelled using two unmatched populations: the EAP population for idebenone and the CaRS-I and CaRS-II natural history populations for SoC. The analysis used to inform on the long-term efficacy and effectiveness of treatment with idebenone is considered by the EAG to be inadequate due to imbalances in prognostic factors in the study populations such as the prevalence of different mutation types and at high risk of bias. Therefore, the long-term efficacy of idebenone remains uncertain.

Further uncertainties arise in the interpretation of long-term evidence from the RHODOS-OFU trial, which was based on a single visit (approximately 30 months after completion of the RHODOS trial), where patients had not been receiving further treatment with idebenone between the completion of RHODOS and their follow-up visit. Although improvements in VA observed for idebenone and placebo after a mean time of 30 months (2.5 years) from week 24 of the RHODOS trial, suggested the benefit of 6 months treatment with idebenone is maintained after treatment is stopped, the lack of intermediate data collection between the end of RHODOS and OFU visit led to uncertainties in the interpretation of results.

Moreover, the EAG notes that overall, in the current evidence, efficacy of idebenone has been documented for up to 5 years after onset and this is highlighted in the CS, with the EAP only including patients with onset of vision loss in the second eye less than 12 months and RHODOS only including patients with onset of vision loss ≤5 years. However, it is noted that the majority of the prevalent population in UK clinical practice will have disease onset >5 years and the EAG has concerns about applicability of results from the trial populations to the prevalent population in UK clinical practice.

Furthermore, there were additional areas of potential bias influencing the interpretation of the evidence. The exclusion of one patient from the placebo group in the mITT analysis of the RHODOS trial, resulted in a considerable increase in the between-group difference, creating uncertainty over the robustness of the RHODOS data. Additionally, given the potential of spontaneous recovery in LHON, there was a risk of overestimating the effect of idebenone.

Finally, it has been noted in existing literature and by clinical experts that the magnitude of the benefit of treatment with idebenone may vary between different subgroups of patients, for example between people with different LHON-causative mDNA mutations. However, limited sample sizes resulting from the clinical trials currently available, did not provide sufficient power to allow for the detection of subgroup effects and support meaningful conclusions about potential differences in the magnitude of the effect of treatment with idebenone between different groups of patients.

4 Cost effectiveness

Table 21 below presents the incremental cost-effectiveness results of the company's updated (i.e., post clarification) base case results.

Table 21. Company's base case results

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,758
Probabilistic results							
SoC	[redacted]	-	[redacted]	-	-	-	-
Idebenone	[redacted]	-	[redacted]	[redacted]	-	[redacted]	19,272

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SoC, standard of care.

*Probabilistic results do not account for idebenone and SoC treatment effectiveness uncertainty

4.1 EAG critique of the company's systematic literature review for cost effectiveness evidence

The company carried out two systematic literature reviews (SLRs) to identify published studies to inform the cost-effectiveness evaluation of idebenone. One SLR aimed to capture publications relevant to cost-effectiveness and costs and resource use, and the other health-related quality of life (HRQoL) associated with Leber's hereditary optic neuropathy (LHON), not limited by intervention. Searches were initially conducted in October and November 2020 with two updated searches being run in February and March 2023. A summary of the External Assessment Group's (EAG's) critique of the methods implemented by the company to identify relevant publications is presented in Table 22. Due to time constraints, the EAG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 22. EAG critique of SLR methods

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix G1.1	Appendix G1.1	Appendix G1.1	Appropriate databases and

				HTA bodies searched.
Inclusion/ exclusion criteria	Appendix G1.1	Appendix G1.1	Appendix G1.1	Appropriate. Exclusion limited to diseases other than LHON.
Screening	Appendix G1.2	Appendix G1.2	Appendix G1.2	Appropriate.
Data extraction	Appendix G1.3	Appendix G1.3	Appendix G1.3	Appropriate.
Quality assessment of included studies	Appendix G1.6	Appendix H1.2	Appendix G1.6	Appropriate. Evaluated using Drummond and Efficace check lists.[44, 45]

Abbreviations: CS, company submission; EAG, External Assessment Group; HRQoL, health related quality of life.

The SLRs identified 10 relevant publications, five of which related to health care resource use and five to HRQoL. None, however, were economic evaluations or contained usable utility values or information that could be used to inform the model. Instead, the company used published NICE technology appraisals in related disease areas (specifically retinal dystrophies and macular degeneration) to inform the development of the *de novo* cost-effectiveness model from a separate targeted literature review.[46-49]

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 23 summarises the EAG's appraisal of the company's economic evaluation against the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.3.

Table 23. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The major health effects for patients with LHON have been included in the economic model.
Perspective on costs	NHS and PSS	All relevant costs have been included and are based on the NHS and PSS perspective.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost-utility analysis has been provided by the company with fully incremental analysis.

Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Lifetime horizon (100 years of age).
Synthesis of evidence on health effects	Based on systematic review	The company has performed an appropriate systematic literature review.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health outcomes have been expressed in terms of QALYs, within HRQoL values taken from Brown *et al*. 1999 which calculated HRQoL values using TTO and a VF-14 questionnaire.[23]
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	HRQoL values obtained from the RHODOS trial were not used in the model. Instead, utilities were informed using Brown *et al*. 1999 which were derived from general population patients.[23]
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The utility data used can be considered relevant to the UK, however they are not LHON specific.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The economic evaluation matches the reference case.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Many of the costs included in the analysis have been sourced using NHS reference costs.[50] However, health state resource use costs have been sourced using Meads *et al.* 2003,[3] which have no clear relation to NHS and PSS costs.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	A discount rate of 3.5% has been used for both costs and health effects.

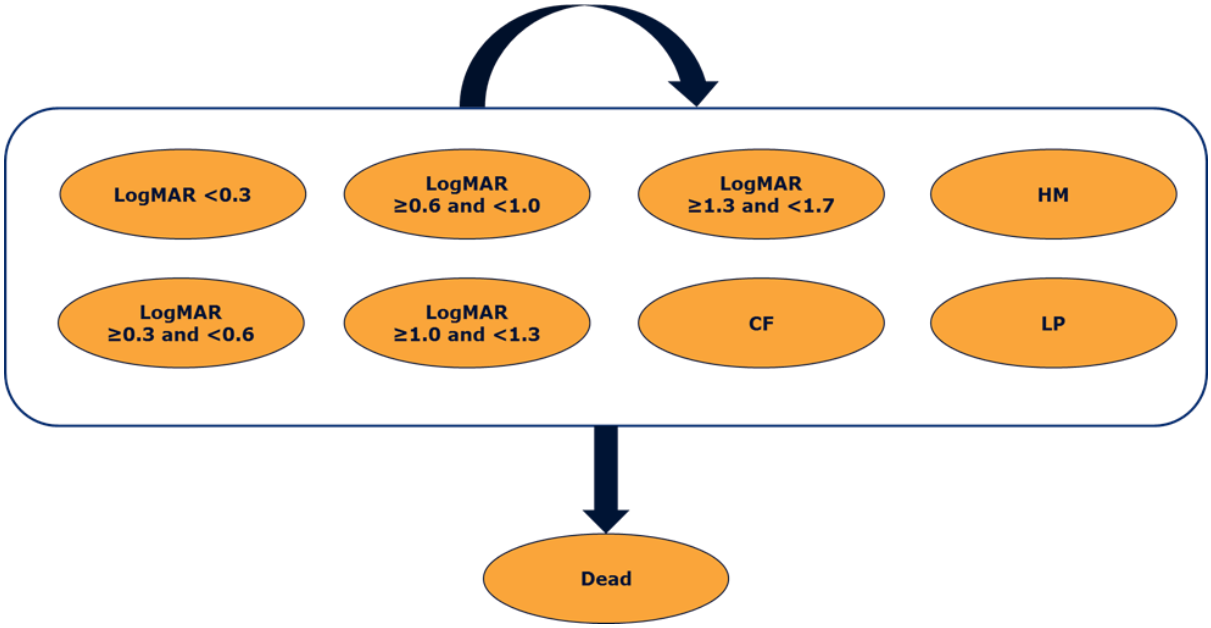
Abbreviations: EAG, External Assessment Group; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year; TTO, time trade off.

4.2.2 Modelling approach and model structure

The company developed a *de novo* Markov model that included eight health states based on visual acuity (VA) expressed in terms of logMAR (logarithm of the Minimum Angle of Resolution), and

death as an absorbing health state (Figure 6). Patients were distributed across the model health states at baseline according to the baseline logMAR distribution of patients in the RHODOS trial.

Figure 6. Company model structure (reproduced from Figure 20 in the CS)



Abbreviations: CF, Counting Fingers; HM, Hand Motion; LP, Light Perception.
NB: CF, HM, and LP correspond to logMAR 2.0, 2.3 and 2.6 in the RHODOS and EAP studies.

The company justified their modelling approach through comparisons to cost-effectiveness models used in previous relevant NICE TAs, specifically HST11 which was conducted in 2019 for voretigene neparvovec in treating inherited retinal dystrophies[46] and NICE TA274[49], TA283[48] and TA298[47] which were conducted in 2013 for ranibizumab across multiple retinal related conditions. A Markov model was used in each approach; however, the models varied considerably between indications, with the HST11 model utilising five health states based on grouped logMAR values according to the American Medicines Association and the NICE TAs using eight or nine health states based on standardised readable EDTRS (Early Treatment of Diabetic Retinopathy Study) bands, which the company's model mirrors.

4.2.2.1 EAG critique

The EAG notes that the company model structure is comparable to NICE TA274[49], TA283[48] and TA298[47] conducted 10 years ago for ranibizumab; however, the EAG considers that a model that groups health states according to key changes in functional sight and HRQoL, similar to the HST11 model,[46] would be more appropriate.

The EAG's clinical experts outlined that patient HRQoL does not perfectly correlate to gain or loss of sight, but instead there are functions and capabilities of sight, which losing or gaining lead to significant changes in HRQoL. Examples of these being the ability to drive (<logMAR 0.3), being eligible for the Certificate of Vision Impairment in England (logMAR >1 [on-chart visually impaired]) and being unable to read any letters on a logMAR chart at six meters (logMAR >1.7 [off-chart visually impaired]). As discussed further in Section 4.2.4, the large number of health states in the economic model also significantly reduces the available patient data to inform each transition probability, leading to health state transitions being impossible and multiple data imputations being required. For example, under both probabilistic and deterministic conditions it is impossible for idebenone treated patients to remain in the Hand Movement health state past cycle 10 (2.5 years) in the company's model. The EAG therefore considers that the company model is flawed and potentially inappropriate for decision making as there is insufficient evidence to support the high number of health states in the economic model given the modest differences in HRQoL and functional capabilities between some of the health states according to the EAG's clinical experts.

While the HST11 model may therefore be preferred to the company model, the health states considered in HST11 conflicted with the opinions of the EAG's clinicians regarding key differences in patient HRQoL according to sight. For example, the HST11 model grouped together patients with logMAR scores of 0 to 1 (Figure 7); however, the EAG's clinical experts argued that a patient with no to limited visual acuities (LogMAR <0.3) will have a significantly higher HRQoL than a patient whose sight has deteriorated to the extent they are no longer able to drive but not considered sight impaired (LogMAR 0.6-1). The EAG's clinical experts also stated that HRQoL would be similar between patients considered off-chart visually impaired (CF, HM and LP) as any sight which may remain is unlikely to provide a level of autonomy.

Following the opinions of the EAG's clinicians, the EAG requested at the clarification stage that the company updated their base case model by grouping the logMAR based health states according to the EAG preferred health states as described in Figure 7. In contrast to the model used in HST11, treatment effectiveness is not capped in the EAG preferred model, allowing patients to have logMAR values and HRQoL utilities more similar to general population estimates. Patients able to drive (limited visual acuities) and unable to drive (moderate visual acuities) are also differentiated. Similarly, logMAR values eligible for the Certificate of Vision impairment in England have been grouped (on-chart visually impaired), and health states unable to read any letters on a logMAR chart (off-chart visually impaired) are also grouped. The EAG additionally considers that that the reduction

in health states also makes the best use of the limited available patient data as it avoids the implausible model transitions exhibited in the company's base-case model.

Figure 7. Company, EAG preferred and HST11 model health states

HST11 health states	Company health states	EAG preferred health states
Moderate visual impairment	LogMAR <0.3	Limited visual impairment
	LogMAR 0.3-0.6	Moderate visual impairment
	LogMAR 0.6-1.0	
Severe visual impairment	LogMAR 1.0-1.3	Visually impaired (on-chart)
Profound visual impairment	LogMAR 1.3-1.7	
CF	CF	Visually impaired (off-chart)
HM, LP	HM	
	LP	

Abbreviations: CF, counting fingers; EAG, external assessment group; HM, hand movement; LP, light perception.

The company did not comply with the EAG's request to update the base case model; however, the company did conduct a scenario using the EAG's proposed model structure. Following the adaptation of the model health states, the health state utility values (HSUVs) and health state resource use estimates were also recalculated to accommodate the changes in model structure, resulting in an increase in the ICER from £18,758 to £27,053. The EAG preferred model structure is assumed in the EAG's base case assumptions.

4.2.3 Perspective, time horizon and discounting

The model cycle length was three months (with a half cycle correction applied) and a lifetime horizon was adopted (up to age 100 years), allowing the model to run for 66 years given a patient starting age of 34 in the model, which was the mean age in RHODOS. The perspective of the analysis was based on the UK NHS and PSS (personalsocial service), with future costs and benefits discounted using an annual rate of 3.5%, as per the NICE reference case.[51]

4.2.3.1 EAG critique

The EAG notes that the half cycle correction applied by the company was calculated as the average of the current and subsequent cycle, applied from the first model cycle (cycle 0); however, the EAG considers the half cycle correction should have been applied to the current and previous cycle from

cycle one onwards. At clarification the company complied with the EAG's request to correct the half cycle correction methodology which led to a £241 increased in the ICER.

4.2.4 Treatment effectiveness

4.2.4.1 Measures of treatment effectiveness and use of the RHODOS trial

The clinical effectiveness of idebenone and SoC (standard of care) treatments were captured by the transitions between health states in the model. Health state transitions probabilities were derived using patient better seeing eye VA observations as this was considered by the company to be the endpoint most relevant to clinical practice and a patient's HRQoL.

The RHODOS study was used to inform the treatment effectiveness for both idebenone and SoC as it was a randomised, doubled-blind, trial comparing idebenone to the current SoC (placebo). However, as the trial length was limited to six months, a period deemed too short to fully demonstrate the full benefits of idebenone by the company, supplementary data were required to model long-term treatment effectiveness.

4.2.4.1.1 EAG critique

The EAG considers that using the treatment effects from RHODOS to inform the idebenone and SoC treatment effect for the first six months of the model is appropriate, as is the use of better seeing eye VA data to derive the transition probabilities.

4.2.4.2 Idebenone long term treatment effects

As described in Section 3.2.3, LEROS and the Expanded Access Programme (EAP) are single-arm open-label studies measuring long term idebenone treatment efficacy. While LEROS is a natural history-controlled intervention study (n=199) conducted over 24 months, the EAP study is a real-world evidence (RWE) non-controlled retrospective analysis (n=87) over 36 months. When deciding which study was most suitable to derive idebenone treated patient transition probabilities post six months (end of the RHODOS study), the EAP study was preferred by the company due to the lesser heterogeneity compared to the LEROS patient populations, with an additional advantage being the longer study time of the EAP.

Compared to the RHODOS study in which 85.9% of patients were male, LEROS contained [redacted]% males with the EAP study containing a more similar 82% male. Additionally, the genetic distribution of the EAP population was more aligned to that of RHODOS than LEROS, with the RHODOS trial only

consisting of idebenone-treated patients who carried three LHON mutations (m.11778G>A [67.3%], m.14484T>C [20%], m.3460G>A [12.7%]), compared to LEROS which consisted of patients from a wider range of LHON mutations (m.11778G>A [redacted], m.14484T>C [redacted], m.3460G>A [redacted], Negative [redacted], Other [redacted]) than the EAP study (m.11778G>A [62.1%], m.14484T>C [18.4%] m.3460G>A [19.5%]). Given that m.14484T>C patients are considered more likely to spontaneously recover by the company and their clinical experts and the difference in the proportion of male patients, the LEROS data were excluded from the economic model with the company preferring to derive transition probabilities from 6 to 36 months using the EAP for the idebenone treated patients.

As a means of validating the use of the EAP, the company compared the six-month outcomes of the RHODOS and EAP studies. The company concluded that the outcomes were broadly similar, with 30.2% (16/53) of idebenone treated patients in RHODOS and 46% (40/87) of patients in the EAP study achieving clinically relevant recovery (CRR) at six months.

After 36 months in the model, the company assumed that patient logMAR VA would stabilise and remain unchanged as this was the opinion provided to the company by their clinical experts. Therefore, patients are modelled to remain in their health state from cycle 12 (month 36) until death in both the idebenone and SoC treatment arms.

4.2.4.2.1 EAG critique

The company preferred to use the EAP over LEROS to derive a long-term treatment effect for idebenone due to the less heterogeneity in genetic distributions and sex proportions. Appendix N (clinical validation) however states that company's clinical experts concluded that the baseline characteristics of the RHODOS, RHODOS-OFU and LEROS trials were all representative of the patient population in clinical practice.

The company aimed to validate using the EAP by comparing CRR achieved at six months between trials; however, the LEROS study outcomes were more comparable to RHODOS than EAP, with [redacted] of LEROS achieving CRR compared to 46% of patients in EAP and 30% of patients in RHODOS. The EAG therefore considers that the RHODOS and EAP outcomes are highly varied with 50% more patients achieving CRR in EAP compared to RHODOS, and notes that LEROS provides more comparable clinical outcomes than the EAP.

In evaluation of CRR as a clinically relevant measure, the EAG notes that as CRR is defined as improvement of at least logMAR 0.2 (equal to two lines of readable letters on a logMAR chart) for

patients with “on-chart” VA at baseline, or an improvement from “off-chart” VA to at least logMAR 1.6 (equal to one line on-chart) for patients with off-chart VA at baseline, CRR may be achieved with no difference in functional sight or change in HRQoL (patients are still considered vision impaired or unable conduct key autonomous function such as driving). Therefore, CRR may not be a helpful indicator of improved HRQoL as it does not differentiate between sight recovery and functional sight recovery. For example, although 30% of idebenone patients achieved CRR in RHODOS after six months, mean recovery in terms of logMAR was 0.037, the equivalent of 1 letter on a logMAR chart.

The EAG is additionally concerned with the use of the EAP dataset over LEROS given the difference in eligible patients in each study. Only patients with symptom onset in the most recently affected for less than one year were included in the EAP study, while patients with symptom onset of less than five years were included in the LEROS study, which was the same inclusion criteria for RHODOS. Given that 44% of LEROS patients had experienced symptom onset for more than one year, if spontaneous recovery is more likely to occur earlier after nadir, then spontaneous recovery would be more likely to occur while being treated with idebenone in EAP than in LEROS, leading to a potential additional confounding of the estimated treatment effect in the EAP.

The LEROS study is also larger than the EAP (196 vs 87 patients) and therefore using LEROS may have lessened the key issue of missing data, which in combination with the high number of health states, leads to multiple transitions between health states in the model being impossible. For example, under both probabilistic and deterministic conditions, idebenone treated patients are unable to move to or remain in the Hand Movement health state past cycle 10 (two and a half years in the model). It’s similarly impossible for any idebenone treated patients to be logMAR 0.3 to 0.6 between cycles 8 and 9.

Even when data is not missing, due to the limited number of patient observations, the transition probabilities are highly uncertain and have far reaching consequences. For instance, the penultimate and final idebenone transition probabilities before VA is assumed to be fixed till death are calculated using only 9 patient observations across the eight health states with three additional imputed observations being required so that transition probabilities can be calculated for all health states.

For these reasons and those outlined in Section 3.2.3, the EAG considers that the LEROS study is more appropriate to inform the idebenone treatment effect after RHODOS, and as such, the company was requested at the clarification stage to conduct a scenario deriving idebenone

transition probabilities using the LEROS ITT population. The company complied with the EAGs request, with the ICER increasing from £18,578 to £21,129 in the scenario.

To validate the use of the LEROS treatment effect in the EAG's base case assumptions, the model mean change in logMAR was plotted against the RHODOS-OFU, LEROS and LEROS natural history matched analysis study findings.

Figure 8 shows that in the scenario using LEROS, logMAR change from baseline is equal to that of the EAP at 6 months as the RHODOS treatment effects are used up to this point. However, after 6 months, the LEROS change in logMAR is less volatile compared to the EAP, possibly due to more patient observations being available in LEROS. The EAP logMAR change from baseline is greater than LEROS and RHODOS-OFU at 36 months (from when logMAR is assumed to be fixed in the model), but the LEROS natural history matched analysis identified a comparable logMAR change after 2 years. The EAG notes that in the natural history matched analysis using LEROS and CaRS patients, no significant difference in logMAR was identified between idebenone and SoC treated patients. For these reasons the idebenone treatment effects from LEROS are assumed in the EAG's base case.

Figure 8. Idebenone mean logMAR change from baseline

4.2.4.3 SoC long term treatment effects

A similar approach was used by the company to select which data should be used to supplement the RHODOS SoC treatment effectiveness in the model. While the company submission (CS) does not explicitly draw on example comparisons between studies as was done between RHODOS, LEROS and EAP for the idebenone treated arm, the company outlined that baseline characteristics of the natural history patients in CaRS-I were similar in terms of age, sex and mutation type to RHODOS and so the study was suitable for deriving SoC transition probabilities in the model.

As data collected in the CaRS-I study had variable follow-up times the company used a "windowing approach" to classify CaRS-I patient observations into 3 months windows. For example, patients with a visit ≥ 1.5 months and < 4.5 months were assigned the 3-month window, while patients with a visit ≥ 4.5 months and < 7.5 months were assigned to the 6-month window. The company used a last observation carried forward (LOCF) approach to control for missing data and imputed the data to allow patients to remain in their health states when no data was available to inform the transition probabilities.

To validate the approach the company compared the proportion of patients who achieved clinically relevant recovery (CRR) at 6 months between RHODOS and CaRS-I, with 10.3% (3/29) of placebo-treated patients in RHODOS and 8.1% of natural history patients in CaRS-I (6/74) achieving CRR. Given the similarity of outcomes at six months, the company therefore concluded that despite some heterogeneity in terms of population and data analysis, CaRS-I was a suitable dataset to model SoC treatment effectiveness after RHODOS.

The company further justified the use of CaRS-I by outlining that the only alternative to using CaRS-I would be to assume no change in VA after six months, thereby using only the measured SoC treatment effects from RHODOS, due to the limited data available.

4.2.4.3.1 EAG critique

While the company outlined their preference for using CaRS-I to derive transition probabilities for the SoC arm, the EAG considers that using CaRS-II or combining CaRS-I and -II studies would have provided a more robust estimate of the SoC treatment effect. As described in Section 3.24, CaRS-II was a retrospective observational study conducted to establish the natural history of LHON patients, specifically aimed to gather data to serve as the natural history comparator group for the LEROS study.

Using the CaRS-II study may have reduced the uncertainty in the treatment effect introduced by the small number of patient observations in the CaRS-I study (n=87), as the CaRS-II population was much larger (n=219). As using the larger CaRS-II study (or a combination of CaRS-I and -II) could reduce the extent of missing data imputation required and the need for LOCF, the EAG requested a scenario that derived a SoC treatment effect using both CaRS -I and -II patients. The company conducted the scenario as requested, using the EAG's preferred model while removing SoC observations generated using LOCF which decreased the ICER to £6,463.

The EAG noted that in the company's scenario, all transition probabilities were informed using only 169 observations, compared to the 740 observations when using CaRS-I and LOCF. In contrast, the company reported in Table 1 of the supplementary clarification response that 944 appropriate and usable observations (from the 5,186 observations recorded in the studies) taken from the 385 appropriate patients from CaRS-I and -II are available. Additionally, individual transition probabilities appear to only be informed by observation from a maximum of 49 patients (the transition probability between months 6 and 9) and a minimum of nine patients (the transition probability from 18 to 21 months). In the scenario the EAG also notes that model mean logMAR is significantly higher than reported in the CaRS -II study. At five years, mean logMAR was approximately 1.64 in the model and 1.06 in the CaRS -II study.

The EAG therefore considers that the SoC treatment effect in the scenario is underestimated and highly uncertain given only a fraction of the patient observations are utilised and the model outcomes do not align to the clinical outcomes. The EAG additionally notes that a more robust treatment effect may be calculated and used in the model should the company have utilised all appropriate and available patient observations from the CaRS studies.

Given the large difference in patient observations when removing observation generated using LOCF, the company was requested to provide the number of SoC observations generated using LOCF used in their base case assumptions. In response the company provided the data in Table 24 .

Table 24. The number of patients whose observations were LOCF at each timepoint in the CaRS-I data (reproduced from Table 22 in the clarification response)

Timepoint	Number of patients whose observations were LOCF at each timepoint (%)
Baseline	0 (0%)
Month 3	21 (28.4%)
Month 6	35 (47.3%)

Month 9	48 (64.9%)
Month 12	59 (79.1%)
Month 15	61 (82.4%)
Month 18	63 (85.1%)
Month 21	66 (89.2%)
Month 24	69 (93.2%)
Month 27	71 (95.9%)
Month 30	70 (94.6%)
Month 33	71 (95.9%)
Month 36	71 (95.9%)

Abbreviations: CaRS, Case Record Survey; LOCF, Last observation carried forward

As shown, at six months where the SoC treatment effectiveness is informed by CaRS-I after RHODOS, almost half of the observations were generated using LOCF. By one year, almost 80% of observations were generated using LOCF, with this proportion increasing to approximately 90% by 21 months. Critically, the transition probabilities that dictate the health state a SoC patient will remain until death are calculated using observations only 4% of which were taken directly from patients at that time. When removing the observations not generated using LOCF, the number of observations used to derive transition probabilities throughout the model using the CaRS-I study falls from 740 to 88. The EAG therefore considers treatment effects associated with using the CaRS-I dataset are highly uncertain and inappropriate with and without LOCF.

Given the EAG consideration that a robust SoC treatment effect may be calculated from the available company data, the EAG requested that the following scenarios be conducted:

- A scenario using all appropriate CaRS-I and -II patient observations available;
- A scenario using the matched natural history patients from CaRS and idebenone LEROS patients, as used to conduct the matched control analysis;
- A scenario using only RHODOS-OFU to model long term treatment effects.

The company did not conduct the requested scenarios, stating that the previously conducted scenario used all available CaRS patient data. Additionally, the natural history matched controlled comparators could not be used due to the matching algorithm being performed *de novo* at each time point. The EAG, therefore, considers that the data are available to conduct a matched analysis but that the company's current matching algorithm is inappropriate for use. Lastly, the company did

not conduct a scenario using the RHODOS-OFU study as the company considered the scenario inappropriate.

As the requested scenarios were not supplied by the company, the EAG conducted an additional scenario. Given that the RHODOS-OFU study showed a maintained difference in change in logMAR from the end of RHODOS (6 months) to the end of RHODOS-OFU (30 months), between idebenone and SoC patients (Figure 15 in the CS), the scenario applied the idebenone transition probabilities from LEROS to SoC patients after RHODOS (see Section 6.3). The EAG consider this approach was preferred to anchoring the idebenone treatment effect to SoC given that the SoC treatment effects from CaRS are highly uncertain. As a means of validating the appropriateness of the scenario, the company base case and scenario mean change in logMAR from baseline results were plotted against the RHODOS-OFU and LEROS natural history matched (CaRS) analysis findings. The RHODOS mITT results were not plotted given the similarity in outcomes to the RHODOS-OFU study (+0.123 and +0.127, respectively).

As seen in Figure 9, SoC patient mean change in logMAR under the LEROS transition probabilities scenario aligns more closely to the RHODOS-OFU results compared to the company base case over time. The figure additionally highlights that although the RHODOS study treatment effects are stated to be applied to SoC patients in the model up to 6 months, change in logMAR from baseline between RHODOS mITT and the model are significantly different, with the mean change in logMAR of SoC patients in the model being 2.28 times worse than measured in the RHODOS trial at 6 months (+0.289 in model vs +0.123 in RHODOS mITT and +0.127 in RHODOS-OFU). If instead considering the RHODOS ITT population outcomes, which as outlined in Section 3.2.1 the EAG deems more appropriate, the model outcomes at 6 months are 3.44 times greater in the model than the trial (+0.289 in the model vs +0.084 in the RHODOS ITT population). The EAG, therefore, includes applying the LEROS treatment effects to SoC patients after the RHODOS treatment effects in its preferred assumptions but caveats that this assumption may be conservative. While at 36 months in the scenario, change from baseline logMAR is slightly better than measured in the RHODOS-OFU trial at 36 months (-0.0065 vs 0.039, respectfully). At the beginning of the model the SoC treatment effect in the LEROS scenario is greatly underestimated compared to the SoC treatment effect in the RHODOS study (6 months) the outcomes of which are less discounted in the model.

The EAG also notes in Figure 9 that the natural history matched analysis showed that SoC logMAR improved over time and was comparable to idebenone logMAR improvement (-0.24 and -0.28, respectively).

Figure 9. SoC mean logMAR change from baseline

The EAG considers it a key issue that company's base case assumptions informing the SoC treatment effect do not replicate the clinical trial findings in the model. Additionally, the EAG considers that a robust SoC treatment effect may be derived from the available CaRS patient data; however, limited patient observations are used from the studies compared to the potentially appropriate and available patient data. Similarly, as reported in Section 3.4.2, alternative matching methodologies could also have been employed to provide more robust treatment effects.

4.2.4.4 Sensitivity analyses

To assess the uncertainty of the idebenone treatment effects on the cost effectiveness results, the company varied the patient observations from the RHODOS and EAP studies, informing the transition probabilities between health states, using a Dirichlet distribution. The same method was not applied to SoC transition probabilities and so the cost effectiveness sensitivity to SoC treatment effectiveness uncertainty was not assessed in any probabilistic sensitivity analysis (PSA) conducted by the company.

4.2.4.4.1 EAG critique

As the model lacked the functionality to allow the SoC treatment effects to be made probabilistic, at the clarification stage the EAG requested that the company allowed the SoC treatment effects to be probabilistic using a similar approach to the idebenone treatment effects. The company however misinterpreted the request, instead removing the probabilistic functionality from the idebenone transition probabilities.

As a follow up clarification question, the EAG requested that both idebenone and SoC transition probabilities be made probabilistic; however, the company did not comply with the EAG's request, stating that, "*including the transition probabilities in the PSA creates substantial uncertainty in the probabilistic results of the CEA. Therefore, the transition probabilities have not been included in the PSA*". The company added that they strongly considered that including the transition probabilities in the PSA will create highly inaccurate probabilistic cost-effectiveness results that will be inappropriate for decision-making. As such, the PSA does not account for treatment effectiveness uncertainty for either idebenone or SoC treatment effects. This is a key issue, as the EAG considers the treatment effects to be highly uncertain given the limited patient data and that the NICE Guide to the Methods of Technology Appraisal states that PSA results are no longer simply recommended but are a mandatory requirement for all cost-effectiveness models submitted to NICE.

4.2.4.5 Treatment discontinuation

All idebenone patients in the model were assumed to experience treatment effects, with no patients experiencing no benefit of treatment. Patients who discontinued idebenone in the model were assumed to continue experiencing idebenone treatment effects and not SoC treatment effects.

4.2.4.5.1 EAG critique

While treatment discontinuation is accounted for in idebenone treatment cost calculations (approximately 40% discontinue treatment after two years), the company's model reflects that no idebenone patients who discontinue treatment go on to experience SoC treatment effects.

The EAP CSR states that of the 111 patients enrolled in the study, 12 patients discontinued treatment due to lack of efficacy, which the EAG considers should be incorporated into the model. When asked at clarification why discontinuation had been applied to treatment costs and not treatment effects, the company noted that although the EAP report v5.0, dated 11 October 2018,

stated that 12 patients out of the 111 patients enrolled did discontinue due to a lack of efficacy, the final EAP report dated 28 August 2019 stated that cumulatively, only nine out of 111 patients permanently discontinued idebenone treatment due to the lack of efficacy, or occurrence of AEs, or a fatal outcome which is captured in the EAP safety population.

The EAG considers that given the transition probabilities are derived from the EAP mITT (n=87) population in the company base case and not the EAP safety population (n=111), patients who experience no treatment benefit with idebenone may not be captured in the model. Similarly, patients who discontinue treatment may not have attended later appointments in the EAP or LEROS studies and so their lack of clinical benefit would not be included as observations in the model. At clarification the EAG requested a scenario exploring treatment discontinuation which the company provided. In the scenario, the company assumed that 4% of patients discontinued idebenone after two years. This proportion of patients was assumed to be in addition to the proportion of patients who discontinue treatment accounted for in the treatment costs and was calculated using a weighted average. The scenario led to an increase in the ICER, from £18,758 to £19,709.

The EAG notes that as the 4% patient treatment discontinuation was made in addition to the patients already discontinuing treatment within treatment costs, treatment costs in the scenario are likely underestimated as patient treatment discontinuation is potentially double counted. Similarly given that 12 of 111 EAP patients discontinued treatment due to a lack of efficacy, the EAG considers the proportion of patients who discontinue treatment in the scenario should be 10.8%. Lastly, patients in the company scenario who discontinue treatment after two years still experience idebenone treatment effects for two years before discontinuing treatment when no treatment effect should be accounted for due to the lack of treatment efficacy.

As such, using the same weighted average approach as the company, the EAG conducted a scenario in which 10.8% of idebenone treated patients incurred idebenone treatment costs and SoC treatment effects for two years before discontinuing treatment (see Section 6.2). The scenario led to an increase in the ICER to £21,022.

4.2.5 Mortality

Mortality assumed for LHON patients was that of all-cause mortality stratified by age and sex using England general population estimates from 2018 to 2020. The company noted that evidence exists demonstrating that the risk of mortality is higher in patients who are visual impaired and therefore

idebenone could be considered to reduce mortality risk compared to no treatment. However, given the lack of specific mortality data for idebenone, the conservative assumption was made to not include a survival benefit for idebenone treated patients.

4.2.5.1 EAG critique

The EAG considers that given the lack of evidence provided for an idebenone survival benefit the company's approach of assuming no survival benefit is reasonable.

4.2.6 Health-related quality of life

4.2.6.1 Health state utility values

The key clinical trials used for measuring the effectiveness of idebenone, discussed in Section 3.2.1, collected condition specific health-related quality of life (HRQoL) data only using the Visual Function Index (VF-14), Clinicians Global Impression of Change (CGIC) and energy levels. The NICE Reference Case[52] recommends the use of EQ-5D-3L directly measured from patients for the estimation of HRQoL. When not available from clinical trial data, EQ-5D data can be sourced from published literature or estimated by mapping from other measures of HRQoL collected in the clinical trials, using published mapping algorithms. No published mapping algorithm is available to map from VF-14, collected in the RHODOS clinical trial, to the EQ-5D. Therefore, the company undertook a systematic literature review (SLR) to identify appropriate health state utility values for use in the economic model.

The company's SLR identified no studies providing utility values for LHON patients that could be used in the economic model. Therefore, the company undertook a targeted literature review to identify utility values based on related diseases and those used in previous NICE TAs (HST 11,[46] TA298,[47] TA283[48] and TA294[53]). Based on the targeted search, the company's base case utility values were based on Brown *et al.* 1999.[23] Brown *et al.* derived utility values using time trade off (TTO) valuation from 325 patients with vision loss due to a range of vitreoretinal diseases, with the majority of patients having either age-related macular degeneration (ARMD) (33%) or diabetic retinopathy (33%). Utility values were provided separately for both the best seeing eye (BSE) and worst seeing eye (WSE), with the company using values for the BSE in their model. Visual acuity was reported across 12 states, represented as a fraction (out of 20 feet), which the company converted to the corresponding logMAR, to match the measurement used in the economic model. As the health states used in the economic model were based on logMAR range as opposed to the point estimate

as presented in Brown *et al.* 1999, the midpoints for each logMAR range used in the economic model were matched up with the closest utility value from Brown *et al.* The utility derived from Brown *et al.* and applied in the company's base-case economic model for each health state are shown in Table 25.

Table 25. LogMAR utility values derived from Brown *et al.* and corresponding model health state utility values (reproduced from Table 26 of the CS)

Brown *et al.* visual acuity	Brown *et al.* utility (95% CI)	Mid-point health state	Model utility value
LogMAR = 0	0.92 (0.87 to 0.97)	LogMAR <0.3	0.84
LogMAR = 0.1	0.87 (0.82 to 0.92)		
LogMAR = 0.2	0.84 (0.79 to 0.89)		
LogMAR = 0.3	0.80 (0.74 to 0.86)	LogMAR 0.3 to 0.6	0.77
LogMAR = 0.4	0.77 (0.70 to 0.84)		
LogMAR = 0.6	0.74 (0.67 to 0.81)	LogMAR 0.6 to 1.0	0.67
LogMAR = 0.7	0.67 (0.57 to 0.77)		
LogMAR = 1.0	0.66 (0.55 to 0.77)	LogMAR 1.0 to 1.3	0.63
LogMAR = 1.2	0.63 (0.54 to 0.72)		
LogMAR = 1.3	0.54 (0.43 to 0.65)	LogMAR 1.3 to 1.7	0.54
CF	0.52 (0.36 to 0.68)	CF	0.52
HM-NLP	0.35 (0.10 to 0.60)	HM/LP	0.35

Abbreviations: CI, Confidence interval; CF, Counting fingers; HM, Hand motion; LP, Light perception; NLP, No light perception

The company also provided alternative utility values identified via the targeted search from Lawrence *et al.* 2023b,[2] Czoski-Murray *et al.* 2009[54] and Rentz *et al.* 2014[55] and provided scenario analyses with these values applied. Following the clarification stage, the company also provided the same sources with the utility values adjusted to match the EAG's proposed model structure using a reduced number of health states, as discussed in Section 4.2.2.

Utility values were not originally adjusted to account for reductions in quality of life with age in the company's economic model. Following a clarification request, the model and company's base-case were updated to include age-adjusted utility values using the Health Survey for England (HSE) 2014 dataset, as recommended by the NICE Decision Support Unit (DSU).[56]

4.2.6.2 EAG critique

In light of a lack of EQ-5D values from the RHODOS trial and no mapping algorithm available from VF-14 collected during the clinical trial, the EAG considers the use of utility values from the literature

to be generally appropriate. However, the EAG notes that details of the targeted search undertaken by the company were not provided and therefore it is unknown if alternative values that may have also been appropriate or relevant are available.

The EAG notes that none of the utility values sourced by the company from the literature use directly reported EQ-5D-3L as preferred in the NICE Reference Case. The utility values used from Brown *et al.*[23] in the company's base case is the only study included by the company that derives utilities from patients, however this was not specific to LHON patients. The majority of patients (66%) in the study had either ARMD or diabetic retinopathy and an average age of 67 years. The EAG notes that the average age of patients from Brown *et al.*[23] is significantly higher than the average age of patients with LHON and the start age of the model (34 years), and patients with ARMD or diabetic retinopathy may have related co-morbidities that could result in utility values not being reflective of LHON patients. In addition, utility values from Brown *et al*. were based on patients from the United States of America (USA).

The company also considered utility values from three alternative studies; Lawrence *et al.* 2023b,[2] Csozki-Murray *et al.* 2009[54] and Rentz *et al.* 2014.[55] Both Csozki-Murray *et al.* 2009[54] and Rentz *et al.* 2014[55] were identified due to being considered in previous NICE TA's (HST 11,[46] TA298,[47] TA283[48] and TA294[53]). The EAG notes Rentz *et al.* provides utilities for eight descriptive health states which were developed based on the Visual Function Questionnaire-Utility Index. For these utility values to be used it would require making assumptions regarding how the health states match up to the equivalent logMAR score. Csozki-Murray *et al.*[54] provided utility values for four health states based on logMAR scores of ≤0.30, 0.31– 0.60, 0.61 – 1.30 and ≥1.31. Based on the grouping of the health states used in the current economic model, the logMAR categories from Csozki-Murray *et al.*[54] may not align well with the health states used, requiring assumptions to be made. The EAG notes that one of the UK clinical experts in the company's validation survey (Appendix N) commented that ([redacted]).

The EAG notes that Lawrence *et al*. 2023b[2] is the only study to provide utility values specifically based on LHON. Although currently only published in poster/abstract form, the EAG considers there is sufficient detail available to review. Lawrence *et al*. 2023a[57] describes the development of eight health state vignettes which varied by level of visual acuity, defined by logMAR score. Draft vignettes

were developed based on literature reviews and trial data and then subsequently revised following feedback from nine LHON patients and five clinicians from the United Kingdom (UK) and Republic of Ireland (ROI). The eight health state vignettes were then valued by 362 members of the public from both UK and ROI using the Health Utilities Index-3 (HUI-3) and EQ-5D-5L via and online survey and a sub-sample of 120 participants also completed TTO interviews. Although referred to in the abstract as EQ-5D-5L health state utility values, it is noted that the EQ-5D-5L data were scored using the Hernandez *et al.*[58] mapping function, which maps to EQ-5D-3L. The EAG confirmed with authors of the study that the EQ-5D-5L data had been mapped to EQ-5D-3L utility values. From the available data, the vignette descriptions seem well defined and used a variety of evidence sources and information to develop them, in line with the NICE DSU recommendations.[59] The NICE DSU report suggests that vignettes should not include value-laden or irrelevant phrases or content, such as "devasting". The EAG does note, however, that the worst health state vignette (logMAR≥4) describes emotional impact of the disease as "*vision loss is devastating, and you find it very difficult to come to terms with*". Although this deviates from the recommendations from the NICE DSU report,[59] the EAG notes that the term 'devasting' is only used in one aspect of the vignette (emotional impact).

The average age of patients completing the valuation survey was 46.5 years old, which is substantially lower than that of the patients used in Brown *et al.* and closer to the average age of patients experiencing LHON. Due to this, and the fact that these values are estimated specifically for LHON and valued by the UK population (and ROI), the EAG considers that this is the most appropriate source of utility values for the economic model. The EAG notes that the choice of valuation method used resulted in wide variation in the utility values estimated for each logMAR health state, as shown below in Table 26, with HUI-3 valuation consistently giving lower utility values. Table 26 also shows the utility values from Lawrence *et al*. 2023b grouped into the EAG's preferred health states, as discussed in Section 4.2.2. from taking the average of the values when grouped. The EAG notes that in Lawrence *et al.* 2023b it is noted that during vignette development interviews, clinical experts discussed the potential overlap between health states and that they were unable to differentiate HRQoL impacts with similar health states. The EAG considers this to be a further validation of using a reduced number of health states.

Table 26. Estimated utility values by logMAR visual acuity, produced based on Figure 2, Lawrence *et al.* 2023b

	HUI-3 (n= 362)	EQ-5D-5L (mapped to EQ-5D-3L)	TTO (n=120)	HUI-3 (n= 362)	EQ-5D-5L (mapped	TTO (n=120)

		(n=358)			to EQ-5D-3L) (n=358)	
LogMAR <0.3	0.837	0.790	0.882	0.837	0.790	0.882
LogMAR ≥0.3 to <0.6	0.511	0.632	0.756	0.473	0.603	0.729
LogMAR ≥0.6 to <1.0	0.435	0.574	0.702			
LogMAR ≥1.0 to <1.3	0.347	0.495	0.565	0.336	0.496	0.545
LogMAR ≥1.3 to <1.7	0.325	0.497	0.525			
LogMAR ~2	0.211	0.368	0.406	0.194	0.352	0.398
LogMAR ~2.3	0.190	0.347	0.426			
LogMAR ~4	0.180	0.341	0.363			

Abbreviations: EQ-5D-5L, EuroQol-5 dimensions-5 level; EQ-5D-3L, EuroQol-5 dimensions-53; level HUI-3, Health Utilities Index-3; TTO, time trade off

Following confirmation from the study authors for Lawrence et al. 2023b[2] that utility values are mapped to EQ-5D-3L, the EAG considers these to be the most appropriate for decision making. Therefore, the EAG's preferred values for their base case analysis is using the EQ-5D values from Lawrence et al. 2023b,[2] with the values using alternative valuation methods applied in scenario analyses (see Section 6.2). The EAG notes that the values applied in the company scenario analysis for Lawrence et al. 2023b, provided as part of the clarification response, differ slightly to those used in the EAG preferred analysis, shown in Table 26, as the EAG has used the values reported for both the UK and ROI due to the larger sample size, whereas the company only reported the values for the UK.

4.2.6.3 Utility decrements

The company applied a lifetime utility decrement of 0.04 for all patients with a logMAR >1.0 to represent the disutility associated with LHON caregivers HRQoL. This disutility is applied for a patient's lifetime. As no quantitative caregiver HRQoL had been collected, the company utilised data from a published systematic review exploring the disutility of caring for an ill or disabled family member, previously used in HST11.[46] The value used by the company is based on a study identified in the systematic review stating that parents of children with activity limitations have a 0.08 lower EQ-5D score than parents of children without activity limitations. The company applied the same approach employed in HST11 and assumed that the disutility of carers of adults with activity limitations would be half of that applied to children.

No adverse events (AEs) disutility was applied in the economic model as, based on the RHODOS trial, most AEs experienced were considered mild.

4.2.6.4 EAG critique

During the clarification stage, the EAG requested that the Company remove the disutility of a caregiver for the proportion of patients who would be in residential care, as these patients would already be receiving separate care service. As part of the clarification response, the Company updated the base-case to remove the carer disutility for the proportion of patients receiving residential care. This had a small impact in the ICER.

The EAG notes that although the same disutility values were applied in HST11 to reflect the impact on caregivers for caring for a family member experiencing blindness, the committee concluded that these values should only be applied to carers of children and not adults and therefore the exclusion of a carer disutility for adult patients was used for decision making. Although the EAG recognises that patients experiencing blindness will require additional assistance from a caregiver, based on the available evidence, the disutility impact on caregivers is uncertain. The EAG preferred analysis applies no caregiver disutility in the base-case, with a scenario analysis provided to explore the impact of its inclusion (see Section 6.2).

4.2.7 Resource use and costs

4.2.7.1 Drug acquisition costs

The list price for idebenone 150mg is £6,364 per pack of 180 tablets. A confidential patient access scheme (PAS) is in place for idebenone (a simple discount of [redacted]) and all results presented in this report include the corresponding PAS. Dosing and subsequent drug acquisition costs in the model follows the SmPC recommended dose of 300mg three times per day. The three month cycle drug acquisition costs are shown in Table 27. The company assumed no administration costs associated with idebenone due to being an oral treatment.

Table 27. Idebenone drug acquisition costs

Dose per day (mg)	Dose per 3 month cycle (mg)	Packs required per cycle	Cost per 3 month cycle (list price)	Cost per 3 month cycle (PAS price)
900	82,181	3.04	£19,370	[redacted]

Abbreviations: mg, milligrams; PAS, patient access scheme

Based on compliance rates observed in the RHODOS trial, the company applies a reduction in drug acquisition costs based on a 96% compliance rate, assumed to apply for the duration of time patients remain on treatment. Patients are assumed to remain on treatment up to three years only, with a proportion of patients discontinuing each cycle based on pooled Kaplan-Meier (KM) treatment duration data observed in RHODOS and EAP, shown in Figure 10. As noted in Section 4.2.4 patients discontinuing treatment affects costs only.

Figure 10. Kaplan Meier curve for time of treatment with idebenone based on RHODOS/EAP data, reproduced from Figure 21 of the CS

As no therapeutic treatments are currently available for LHON, SoC is assumed to consist of established clinical management which includes visual aids, low vision rehabilitation and lifestyle management. No separate treatment costs are assumed to apply for SoC as this is instead captured in the health state resource use costs and also applied to patients on idebenone.

4.2.7.1.1 EAG critique

Clinical experts outlined to the EAG that they may continue to treat patients up to three years and beyond if patients were responding to treatment or had only recently stabilised. In addition, within the EAP study, treatment duration ranged from 2.4 – 70.4 months. During the clarification stage, the

EAG requested that the company extrapolated the time on treatment KM data using parametric curves to inform treatment costs for idebenone patients beyond three years. The company stated that due to the low patient numbers available beyond three years, extrapolating these data would be highly uncertain and inappropriate. In addition, it was noted that as clinical data is only measured up to three years, extrapolating time on treatment data beyond this time point would be biased against idebenone as costs are accrued without clinical benefit.

Although the EAG agrees that there are limited patient numbers available to produce meaningful extrapolations, it is noted that in years 2–3 of the economic model, idebenone patients are still moving between health states and improving, suggesting that patients may not yet have stabilised. As clinical experts suggested to the EAG that they may continue to treat patients who recently stabilise, and two of the company's UK clinical experts stated they would treat until stabilisation or plateau, the EAG considers that in clinical practice treatment costs will continue to be accrued for recently stabilised patients beyond three years. Therefore, the EAG considers it plausible for treatment costs to continue beyond the three year time period despite patients no longer moving between health states in the economic model. Not applying any treatment costs beyond this period may underestimate the true costs and is an area of uncertainty in the economic model. However, the EAG does not consider there to be robust data available to estimate the duration of treatment costs beyond three years.

As noted in Section 4.2.4, the EAG considers that LEROS is the more appropriate study to inform the idebenone treatment effectiveness after RHODOS, compared to EAP used by the company. However, as LEROS was conducted over a shorter time period than EAP (up to two years only), treatment discontinuation is curtailed by the shorter study duration. Therefore, the EAG considers the use of the LEROS data to inform treatment effectiveness, with EAP data used to inform the time on treatment to be more appropriate. Despite the EAG considering that patients may continue to receive treatment past three years, the use of the longer-term EAP time on treatment data (up to three years) is assumed to provide an illustration of using a longer treatment duration when combined with the LEROS data used for treatment effectiveness.

4.2.7.2 Routine monitoring

In line with their clinical expert opinion, the company applied the cost of an ophthalmologist visit three times per year for patients treated with idebenone for the first year of treatment, followed by one visit per year for subsequent years. This was based on their clinical expert opinion stating that

they would expect to see patients on idebenone every 4–6 months in the first year. For patients on SoC, this was assumed to be once per year for the entire duration of the model. Annual resource use was converted to every three months to match the cycle length of the model.

4.2.7.2.1 EAG critique

The EAG's clinical experts stated that patients with LHON would have optical coherence tomography (OCT) undertaken each time they had an outpatient visit with ophthalmology. Similarly, the EAG noted the cost difference between first and follow-up attendance for ophthalmology visits in the NHS Reference costs. Therefore, at the EAG's request during the clarification stage, the company updated the costs of ophthalmology to use a separate cost associated with first visit and follow-up visits, while including the cost of an OCT alongside every ophthalmology visit and updated their base-case results to reflect this, resulting in a small increase in the ICER of £96. The final resource use and costs associated with routine monitoring in the model are shown in Table 28.

Table 28. Routine monitoring costs and resource use

Resource	*Unit cost*	*Per cycle resource use: idebenone (cycle 1-4)*	Per cycle resource use: idebenone (cycle 5+) and SoC	*Source*
Ophthalmology visit (first visit)	£166.64	0.75	0.25	NHS reference costs 2021/2022. outpatient care - Ophthalmology service, Non-Admitted Face-to-Face Attendance, First
Ophthalmology visit (subsequent visit)	£143.93			NHS reference costs 2021/2022. outpatient care - Ophthalmology service, Non-Admitted Face-to-Face Attendance, Follow-up (WF01A)
OCT	£158.23			NHS reference costs 2021/2022. Retinal Tomography, 19 years and over' (BZ88A)

Abbreviations: NHS, National Health Service; OCT, optical coherence tomography; SoC, standard of care

4.2.7.3 *Health state resource use*

The company included costs for each health state, assumed to represent the costs associated with blindness, varying by logMAR score. The included resources associated with blindness were informed from a published study by Meads et al. 2003,[3] used in previous NICE appraisals for eye conditions (HST11,[46] TA155,[60] TA294[53] and TA274[49]). The company's included resource use consisted of hospitalisations (assumed to be due to injurious falls), outpatient visits (obtaining low vision aids and rehabilitation), blind registration, supportive living, residential care (aged 65+ only) and depression. Both blind registration and depression were assumed to be one-off costs applied in the first year, whereas all other costs are assumed to occur per cycle.

The company stated that as Meads et al.[3] was based not specifically on patients with LHON and rather in an older population of patients strictly classed as blind, as such the reported resource use was not applicable to the LHON population. They therefore obtained estimates of each resource use across the included model health states, classified by logMAR value, from a survey [redacted]. The average of the estimated resource use from the [redacted] was then calculated and these estimates were validated by five UK clinical experts.

The unit costs for hospitalisations due to injurious falls was assumed to be the cost of an A&E visit, sourced from NHS Reference Costs 2021/22. All other included costs were taken from Meads et al. and inflated from 2001 prices to 2022 using the Personal Social Services Research Unit (PSSRU) hospital and community health service (HCHS) pay and price indices. Following a clarification request from the EAG, the company updated the cost used for residential care to be sourced from PSSRU 2022 rather than inflated from Meads et al.[3] Resource use and unit costs applied in the company's model are shown in Table 29 and Table 30, respectively.

Table 29. Resource use for each health state defined by logMAR used in the company's model

Resource	Health state resource use							
	LogMAR <0.3	LogMAR 0.3 to 0.6	LogMAR 0.6 to 1.0	LogMAR 1.0 to 1.3	LogMAR 1.3 to 1.7	CF	HM	LP
Hospitalisations	2%	3%	10%	18%	20%	22%	27%	30%
Outpatient visits	13%	38%	80%	83%	83%	83%	83%	83%

Blind registration*	0%	25%	78%	100%	100%	100%	100%	100%
Supportive living	0%	0%	20%	40%	48%	57%	63%	70%
Residential care (age 65+)	0%	2%	7%	7%	8%	20%	22%	35%
Depression due to LHON onset	7%	20%	30%	33%	42%	45%	58%	65%

Abbreviations: CF, counting fingers; HM, hand motions; LHON, Leber hereditary optic neuropathy; LP, light perception

* Applied in the first year only (cycles 1 to 4)

Table 30. Unit costs for health state resource use applied in the company's model

Resource	Unit cost from Meads (2000 prices)	Annual (inflated to 2022)	Per cycle	Source
Hospitalisations	-	£1,728.82	£432.20	NHS Reference Costs 2021/2022: Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment (VB02Z) Cost representing hospitalisation due to falls
Outpatient visits for low vision	£341.63	£577.26	£144.31	Cost from Meads et al. inflated using PSSRU Cost representing low vision aids (£136.33) and low vision rehabilitation (£205.30)
Blind registration	£97.41	£164.74	£41.18*	Cost from Meads et al. inflated using PSSRU. Cost representing doctor's sessional fee for completing Certificate of Vision Impairment (59.70) and mean cost of a community occupational therapist for the initial assessment (£37.71)
Supportive living	£2,848.63	£4,818.23	£1,204.56	Cost from Meads et al. inflated using PSSRU Cost representing community home care worker
Residential care (age 65+)	-	£75,241.50	£18,810.38	PSSRU 2022. Local authority own-provision residential care for older people (age 65+)
Depression due to LHON onset	£391.97	£662.90	£165.72*	Cost from Meads et al. inflated using PSSRU. Cost representing costs depression due to the onset of LHON

Abbreviations: LHON, Leber hereditary optic neuropathy; NHS, national health service; PSSRU, Personal Social Services Research Unit

* Applied in the first year only (cycles 1 to 4)

In response to a clarification question (question B1), the company also provided the proportion of patients requiring each resource when using the EAG's preferred modelled health states, as discussed in Section 4.2.2. The estimates for the updated health states were calculated by taking the average of the proportions from the combined health states, reported below in Table 31.

Table 31. Company resource use estimates applied to the EAG preferred model structure

Resource	Limited visual acuities (logMAR <0.3)	Moderate visual acuities (logMAR 0.3 to 1.0)	On chart visual acutities logMAR 1.0 to 1.7	Off-chart visual acuities (logMAR >1.7)
Hospitalisations	2%	7%	19%	26%
Outpatient visits for low vision	13%	59%	83%	83%
Blind registration	0%	52%	100%	100%
Supportive living	0%	10%	44%	63%
Residential care (age 65+)	0%	4%	8%	26%
Depression due to LHON onset	7%	25%	38%	56%

Abbreviations: LHON, Leber hereditary optic neuropathy

4.2.7.3.1 EAG critique

The EAG notes that it is not aware of any published literature available on resource use for patients with LHON specifically, hence why the company used estimates derived from clinical experts. The resource categories included for health state costs were informed by Meads *et al.* [3] which, as previously stated, has been used in numerous NICE TAs. The EAG notes that in previous NICE TAs (HST11,[46] TA155[60] and TA294[53]), the proportion of patients expected to require each resource is taken directly from Meads *et al.* and applied to patients who are classified as blind, dependent on the visual acuity measure used in the economic models.

During the clarification stage, the EAG requested that the company included a scenario analysis using the proportion of patients requiring each resource taken directly from Meads *et al.* and applied only to patients with a logMAR >1. In response to clarification, the company included a scenario analysis using data from Mead *et al.* However, within this scenario, the company deemed it inappropriate to assume patients with logMAR<1 do not require any resource use and therefore

applied the same proportions obtained from their clinical experts for these health states. In addition, the company stated that as the proportion of patients requiring hospitalisation in Mead *et al.* reflects patients requiring a hip replacement rather than due to injurious falls in their own model, the proportions for hospitalisations estimated from their clinical experts is still applied in this scenario. The company noted that the estimated proportions reported in Meads *et al.* represents an elderly population which does not align with the LHON population in this current appraisal. The EAG notes that many of the estimated proportions used by the company are actually higher than those estimated by Meads *et al.* Clinical experts advising the EAG suggested that as LHON typically occurs in a younger population, patients often adapt to their eyesight, more so than if it had developed later in life. Therefore, it might be more likely that the resource use proportions in Meads *et al.* representing an older population are higher than that for the LHON population.

While the EAG agrees that the proportions estimated in Meads *et al.* may not be fully reflective of the younger LHON population, the EAG considers the proportions used in the company's base-case to be highly uncertain. The EAG notes that in the initial survey of [redacted], from which the resource use estimates were obtained, there was often a wide range between the highest and lowest estimates provided for many resource categories. The company then presented the averages of the three experts to five UK clinical experts for validation. The company reported that one clinical expert stated that they would expect outpatient care to be higher and therefore ran a scenario analysis in which this was 2 times higher. However,

[redacted]

The EAG clinical experts also provided comments on the resource use proportions included in the model. One expert stated that they would not expect young people with vision equal to driving vision to be experiencing regular falls, as estimated by the company's resource use. In response to a clarification question (B16b), the company referenced a study undertaken by the Royal Institute of Blind People (RNIB), reporting that 8,021 falls related to partial sightedness and blindness occurred in patients aged 18-59. The company also stated that the report estimated that half of fallers have reoccurring falls, thus supporting the application of hospitalisations as a regular per cycle cost in the economic model. While the EAG considers it plausible that a proportion of patients may have regular falls requiring hospitalisation, it is uncertain if this would apply to patients with good visual acuity,

every 3 months for the entire model duration, despite only being applied to a small proportion. The EAG, therefore, considers it more plausible to apply the proportion of patients requiring hospitalisation from Meads *et al*. to all patients with a logMAR >1 and assume that this proportion is representative of patients requiring hospitalisation due to injurious falls.

The cost of supportive living from Meads *et al.* 2003 used in the company's model is assumed to reflect the cost of a community home care worker. A clinical expert advising the EAG noted that they expect this would entail assessing the home environment and installing features that may help. It was noted that this would generally be a one-off visit rather than a regular on-going cost.

Clinical experts also stated to the EAG that supplying low vision aids, in the form of magnification tools and rehabilitation would not be an ongoing regular cost throughout a patient's lifetime but more of a one-off cost required on sight deterioration (likely when considered sight impaired [logMAR>1]). Following a request during the clarification stage, the company provided a scenario in which outpatient care costs were applied as a one-off costs rather than per cycle. The EAG deem this to be more reflective of clinical practice and applies this in the EAG preferred analysis (see Section 6).

Due to the uncertainty in the company's estimates derived from their clinical experts and a lack of available evidence for resource use in the LHON population, the EAG considers it more appropriate to use estimated resource use from Meads *et al.*, applied to patients with a logMAR>1. However, as the cost of depression is applied as a one-off cost, the EAG considers it more appropriate to apply the proportion of patients experiencing this cost to all health states as clinical experts advised that this is likely to affect all patients with a diagnosis of LHON as they adjust to their prognosis. Meads *et al.* reported separate resource use for low vision aids (11%) and low vision rehabilitation (33%); however, the company's model structure combined these into one resource use (Outpatient visits for low vision). Therefore, in order to implement the Meads *et al*. proportions in the company's model it was necessary to take the average of low vision aids and low vision rehabilitation (22%). As both the low vision aids and rehabilitation had similar costs (see Table 30), the EAG does not consider this will have a considerable impact. The EAG's preferred assumptions are summarised below and Table 32 shows the EAG's preferred resource use estimates in line with the EAG's preferred model structure:

- Proportion of patients requiring each resource sourced from Meads *et al.* 2003, applied only to patients with logMAR>1, except depression costs which are assumed to apply to all health states.
- Costs for outpatient visits for low vision (vision aids and rehabilitation), blind registration, supportive living and depression all applied as a one-off cost in the first year.
- Proportion experiencing hospitalisation assumed to be applicable to those having injurious falls.

Table 32. EAG preferred resource use assumptions applied to EAG preferred model health states

Resource	Limited visual acuities (logMAR <0.3)	Moderate visual acuities (logMAR 0.3 to 1.0)	On chart visual acuities logMAR 1.0 to 1.7	Off-chart visual acuities (logMAR >1.7)
Hospitalisations	0%	0%	5%	5%
Outpatient visits for low vision	0%	0%	22%	22%
Blind registration	0%	0%	95%	95%
Supportive living	0%	0%	6%	6%
Residential care (age 65+)	0%	0%	30%	30%
Depression due to LHON onset	39%	39%	39%	39%

Abbreviations: LHON, Leber hereditary optic neuropathy

5 Cost effectiveness results

5.1 Company's cost effectiveness results

Table 33 presents the cost-effectiveness results of the company's updated (i.e., post clarification) base case deterministic and probabilistic analyses. The probabilistic sensitivity analysis (PSA) conducted to assess the joint parameter uncertainty around base case results used a Monte Carlo simulation and derived probabilistic results from 1,000 generated simulations. The EAG notes that as described in Section 4.2.4, transition probabilities were not made probabilistic in the PSA and so treatment effectiveness uncertainty has not been accounted for. Therefore, while probabilistic results have been provided, the EAG considers these results may be inappropriate for decision making given the extent of the treatment effectiveness uncertainty.

Table 33. Company's base case results

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,758
Probabilistic results*							
SoC	[redacted]	-	[redacted]	-	-	-	-
Idebenone	[redacted]	-	[redacted]	[redacted]	-	[redacted]	19,272

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SoC, standard of care.

*Probabilistic results do not account for idebenone and SoC treatment effectiveness uncertainty

A PSA scatterplot is presented in Figure 11 and a cost-effectiveness acceptability curve (CEAC) is presented in Figure 12. Based on these analyses, the probability that idebenone is cost effective versus SoC is 50% at a willingness to pay (WTP) threshold of £20,000 and 85% at £30,000, using the company base case assumptions.

The EAG notes that as the idebenone and SoC treatment effects have not been varied according to uncertainty in the estimated treatment effectiveness, the deterministic results may be considerably different from the probabilistic results.

Figure 11. Company base case PSA case scatter plot

Figure 12. Company base case cost-effectiveness acceptability curve

5.2 Company's sensitivity analyses

5.2.1 One-way sensitivity analysis

The company conducted a one-way sensitivity analyses (OWSA) to assess the sensitivity of the ICER to varying specific parameters in isolation and to identify the main model drivers. The results are illustrated in Figure 13. The EAG notes that while the ICER was most sensitive to the utility of patients with a logMAR of less than 0.3, the analysis did not vary treatment effectiveness which the EAG considers the ICER may be most sensitive to given the results of the EAG scenario conducted.

Figure 13. Company base case one-way sensitivity analysis

5.2.2 Scenario analysis

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters, in addition to several scenario analyses requested by the EAG. Results of all scenario analyses conducted by the company are presented in Table 34.

Table 34. Company conducted scenario analyses

Parameter	Scenario number	Base-case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
Discount rate for costs and outcomes	1	3.5%	0%	[redacted]	[redacted]	2,929
	2		1.5%	[redacted]	[redacted]	9,964
	3		6%	[redacted]	[redacted]	34,074
Time horizon	4	66 years	50 years	[redacted]	[redacted]	21,375
	5		30 years	[redacted]	[redacted]	29,754
Utility source	6	Brown *et al.* (1999)	Rentz *et al.* (2014)	[redacted]	[redacted]	18,787
	7		Lawrence *et al.* – EQ-5D-5L	[redacted]	[redacted]	22,070
	8		Lawrence *et al.* – HUI3	[redacted]	[redacted]	15,680
	9		Lawrence *et al.* – TTO	[redacted]	[redacted]	18,714
	10		Czoski-Murray *et al.*	[redacted]	[redacted]	20,094
Baseline characteristics source	11	RHODOS	EAP	[redacted]	[redacted]	20,333
	12		CaRS	[redacted]	[redacted]	19,224
	13		Pooled RHODOS, EAP and CaRS	[redacted]	[redacted]	19,484
Caregiver disutility	14	Included	Excluded	[redacted]	[redacted]	22,181
Compliance	15	RCT compliance	Full compliance – 100%	[redacted]	[redacted]	21,453
	16		RWE compliance – 87%	[redacted]	[redacted]	17,454
Resource use inputs	17	Informed by KOL survey (2022) with the exception of ophthalmologist visits	Base-case + outpatient care use adjusted according the UK clinical input	[redacted]	[redacted]	21,615

Using the EAG's proposed health states	B1	Company preferred model	EAG preferred model	[redacted]	[redacted]	27,053
Applying the LEROS data from month 6 to month 24 in the idebenone arm	B2	EAP	LEROS	[redacted]	[redacted]	21,129
Removing the LOCF assumption from the CaRS data	B3	Using LOCF	No LOCF	[redacted]	[redacted]	1,963
Applying a 4% idebenone treatment discontinuation rate for idebenone	B8	No discontinuation rate applied to treatment effect	Discontinuation rate applied to treatment effect	[redacted]	[redacted]	19,709
Applying various HRQoL sources using the EAG's proposed health states	B10	Company preferred model	EAG preferred model	[redacted]	[redacted]	19,107 – 29,407
Applying a one-off outpatient care cost for idebenone	B16	Recurring outpatient care cost	One-off outpatient care cost	[redacted]	[redacted]	19,595
Applying the adjusted resource use inputs based on Meads et al.	B20	Additional health care resource use for those not visually impaired	No additional health care resource use for those not visually impaired	[redacted]	[redacted]	22,277
Using the EAG's proposed health states with LEROS data for idebenone	B21	Company preferred model, EAP	EAG preferred model, LEROS	[redacted]	[redacted]	26,798

Abbreviations: CI, confidence intervals; CaRS, Case record survey; EAG, external assessment group; EAP, Extended access programme; LOCF, last observation carried forward; NHS, National Health Service; PSA, probability sensitivity analyses; PSS, Personal social services; RWE, Real-world evidence; SE, standard error

5.3 Model validation and face validity check

The company states that the cost-effectiveness model was quality assured by a senior health economist not involved in the model build who reviewed the model for coding errors, inconsistencies, and plausibility of inputs and outputs. The company also states that the model was subject to stress testing of extreme scenarios to test for technical modelling errors and plausibility of results.

6 Additional economic analysis undertaken by the EAG

6.1 Model corrections

The External Assessment Group (EAG) did not identify any model errors requiring correction.

6.2 Exploratory and sensitivity analyses undertaken by the EAG

In Section 4 of this report, the EAG has described several scenarios that warranted further exploration in addition to the company's own sensitivity and scenario analyses. The EAG cost effectiveness scenarios comparing idebenone to SoC (standard of care) are listed below, with results presented in Section 6.3.

- Applying the idebenone LEROS transition probabilities to SoC patients after RHODOS – Section 4.2.4;
- Adjusting the idebenone treatment discontinuation weighted average calculation and increasing the proportion who discontinue treatment to 10.8% – Section 4.2.4;
- Adjusting the EQ-5D utilities calculated from Lawrence *et al.*[2] to include patients from the Republic of Ireland – Section 4.2.6;
- Applying healthcare resource costs associated with visual impairment according to Meads *et al.*[3] – Section 4.2.7;
- Applying supportive living cost as a one-off cost – Section 4.2.7;
- Applying outpatient care cost as a one-off cost – Section 4.2.7.

6.3 EAG scenario analysis

All additional scenarios conducted by the EAG were done so using the EAG's preferred model structure. The results of EAG scenarios are outlined in Table 35.

Table 35. Results of the EAG's scenario analyses

	Results per patient	Comparator	Intervention	Incremental value
-	Company base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	18,758
0	EAG preferred model structure			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]

	ICER (£/QALY)	-	-	27,053
1	Applying the LEROS transition probabilities to SoC patients after RHODOS			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	59,061
2	Adjusting the idebenone treatment discontinuation weighted average calculation and increasing the proportion who discontinue treatment to 10.8%			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	30,316
3	Adjusting the EQ-5D utilities calculated from Lawrence *et al.*[2] to include patients from the Republic of Ireland			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	27,780
4	Applying additional healthcare resource costs according to Meads *et al.*[3]			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	31,631
5	Applying supportive living cost as a one-off cost			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	35,456
6	Applying outpatient care cost as a one-off cost			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	28,128

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

6.4 EAG preferred assumptions

Table 36 outlines the EAG's preferred assumptions and the independent and cumulative impact on the ICER of each assumption. The EAG's base case deterministic and probabilistic cost-effectiveness results are provided in Table 37.

- EAG preferred model structure;
- Using the LEROS study to derive the idebenone long term treatment effects;

- Applying the idebenone transition probabilities to SoC patients after RHODOS;
- Adjusting the idebenone treatment discontinuation weighted average calculation and increasing the proportion who discontinue treatment to 10.8%;
- Using the EQ-5D utilities calculated from Lawrence *et al.*[2] that include patients from the Republic of Ireland;
- No carer disutility applied;
- Applying additional healthcare resource costs according to Meads *et al.*[3] ;
- Applying supportive living cost as a one-off cost;
- Applying outpatient care cost as a one-off cost.

Table 36. EAG preferred model assumptions

Preferred assumption	Section in EAG report	Independent ICER (£/QALY)	Cumulative ICER (£/QALY)
Company base case	-	18,758	18,758
EAG preferred model structure	4.2.2	27,053	27,053
Using the LEROS study to derive the idebenone long term treatment effect*	4.2.4	28,459	35,736
Applying the LEROS transition probabilities to SoC patients after RHODOS	4.2.4	59,061	99,366
Adjusting the idebenone treatment discontinuation weighted average calculation and increasing the proportion who discontinue treatment to 10.8%	4.2.4	21,022	111,280
Using the EQ-5D utilities calculated from Lawrence et al[2] that include patients from the republic of Ireland**	4.2.6	27,780	109,432
No carer disutility applied	4.2.6	21,019	127,207
Applying additional healthcare resource costs according to Meads et al.[3]**	4.2.7	31,631	128,419
Applying supportive living cost as a one-off cost	4.2.7	25,899	129,704

Applying outpatient care cost as a one-off cost	4.2.7	19,595	130,269

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

*EAP discontinuation rate applied given the limited LEROS study duration

**EAG preferred model structure assumption also required

Table 37. EAG base case results

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	130,269
Probabilistic results*							
SoC	[redacted]	-	[redacted]	-	-	-	-
Idebenone	[redacted]	-	[redacted]	[redacted]	-	[redacted]	126,422

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SoC, standard of care.

*Probabilistic results do not account for idebenone and SoC treatment effectiveness uncertainty

6.5 Conclusions of the cost effectiveness sections

Overall, the EAG considers that many of the company's assumptions informing the economic model are bias in favour of idebenone, leading to its cost-effectiveness being overestimated.

Structurally the company's model does not align with key HRQoL sight related thresholds outlined by the EAG's clinical experts and the high number of health states used in the company's base case lead to health state transitions being impossible when coupled with the equally critical issue of the small number of patient observations informing the model.

Of all the issues identified by the EAG in the company's model, the EAG considers the modelling of the SoC treatment effect is the most impactful. The EAG has identified that SoC logMAR recovery is considerably worse in the model than in the RHODOS, RHODOS-OFU and the LEROS natural history matched analysis, with SoC logMAR worsening 2.28 times as much in the model compared to the end of the RHODOS study (6 months) if considering the mITT population and 3.84 worse with respect to the ITT population. Additionally, while the RHODOS OFU and CaRS -II studies recorded that mean SoC logMAR recovered to baseline values by three and four years respectively, these results are also not reflected in the model.

While limited available patient data is a key issue in many health technology assessments with rare genetic conditions influencing the ability of companies to provide a robust SoC treatment effect, the EAG considers that there appears to be sufficient trial data to inform a robust SoC treatment effect, which the company has not utilised. For example, the EAG requested a scenario which utilised all available and appropriate CaRS patient data (approximately 944 observations); however, only 169 observations were used in the scenario. The EAG, therefore, considers that the modelled SoC treatment effect is underestimated and highly uncertain.

The company has additionally failed to account for the uncertainty in the estimates of treatment effectiveness within their deterministic and probabilistic sensitivity analyses (PSA). While the company has attempted to justify the exclusion of treatment effectiveness uncertainty from the sensitivity analysis by suggesting it's inclusion will create substantial uncertainty in the results, the EAG considers this a critical flaw in the development of the model. Investigating the impact of parameter uncertainty on the incremental cost effectiveness ratio (ICER) is a critical step in the evaluation of new health technologies. The NICE Guide to the Methods of Technology Appraisal states that PSA results are no longer simply recommended but are a mandatory requirement for all cost-effectiveness models submitted to NICE.

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8 Appendices

8.1 Quality assessment

Table 38. Quality of effectiveness estimates from non-randomised studies (QuEENS) checklist for the propensity score matching (PSM) analysis of LEROS ITT idebenone-treated patients compared to CaRS SoC treated patients.[43]

Question	Answer
Q1: Have different methods been compared within the study?	No - Only a single method, propensity score matching, was used
Q2: Have the results of the study been compared to others in the literature?	Not compared – no other estimates were available
Q3: Is there a discussion of what treatment effect is identified and of the assumptions needed?	No discussion of either
Q4: Is the model chosen consistent with the outcome variable if using a parametric method?	Yes/unclear. ANCOVA is used but no justification was provided. LogMAR values from LEROS included those measured in a continuous fashion through ETDRS charts, and ordinal measurements of "finger counting", "hand motion" and "light perception". The distribution of logMAR values was presented as binned categories, but skewness was not assessed. LogMAR values from the CaRS studies were converted from Snellen measurements.
Q5: Were any checks conducted on the model specification?	No checks reported
Q6: On selection: Is the assumption of selection on observables assessed?	Partially, the EAG suggested some key baseline characteristics for matching, to which the Company added others, albeit without explicit justification or discussion of whether any prognostic factors were unmatched and/or not available.
Q7: What checks were conducted to assess overlap?	No checks reported, although there was a reasonable degree of overlap for each baseline characteristic between unmatched populations.
Q8: Has balancing of the covariates been checked after matching and propensity score methods?	Yes, through standardised mean differences presented in Figure 1 of Company response to clarification.
Q9: Is the propensity score function sufficiently flexible?	Unclear/unlikely to be sufficiently flexible, it was not reported that polynomial or interaction terms were allowed for in the calculating of the propensity score.
Q10: Are potential IVs excluded from the set of conditioning variables?	Yes, other than sex, each variable included in the matching set is likely a meaningful prognostic factor
Q11: Data quality: Are there data quality issues?	(a) Data and definitions comparable for treated and control groups: Partially, logMAR values directly measured in LEROS but are converted Snellen measures in CaRS;

	(b) Treated and controls come from the same area or environment: No, CaRS is a historical natural history study whereas LEROS a clinical trial; (c) Rich set of variables used for matching: Yes, a reasonable set of variables were used for matching; (d) Reasonable sample sizes: Partially, given the rarity of the disease the sample sizes appear reasonable, despite no formal consideration of statistical power in the matched-control analysis. However, the EAG is concerned that only a single time point (24 months) was used from the follow-up data.
Q12: For Nearest Neighbour: Has bias adjustment been conducted if more than one variable was included when matching on covariates?	No bias adjustment was reported.
Q13: Is the choice of replacement (with/without) reasonable?	Partially, the decision was not justified but most NH patients were successfully matched without replacement.
Q14: Is the choice of the number of calliper matching reasonable?	Yes, a standard calliper width was used that did not result in an excessive loss of sample size.[61]

Abbreviations: ANCOVA, analysis of covariance; EAG, external assessment group; ETDRS, Early Treatment of Diabetic Retinopathy Study; logMAR, logarithm of the minimum angle of resolution; NH, natural history

Single Technology Appraisal

Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 7 February 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Long term treatment effect

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.1., Page 14, Table 1 "*There is no precise effectiveness estimate for treatment with idebenone beyond six months to draw robust conclusions about its long-term clinical and cost-effectiveness"* The EAG consider there to be no precise long-term term effectiveness for treatment with idebenone, despite supportive evidence from the Phase 4 LEROS trial and the EAP RWE study.	The Company ask for text to be modified to ensure that the text is balanced as follows: "*There is no* ***~~precise~~*** *effectiveness estimate for treatment with idebenone beyond six months* ***from an RCT*** *to draw robust conclusions about its long-term clinical and cost-effectiveness".*	The company believes that while there are no RCTs with data beyond 6 months the LEROS and EAP studies provide strong, supporting evidence on the long-term effectiveness of idebenone. The EAP demonstrated that long-term treatment duration with idebenone results in a higher rate of responders with a greater magnitude of improvement in recovery. A CRR from nadir was achieved in 46% of patients, and 50% of patients achieved a CRS. For patients with a CRS, mean BCVA improved by +9 letters on the ETDRS chart from baseline to last visit.(1) Similarly, in LEROS, a trial designed with guidance and approval from the EMA, a longer treatment duration demonstrated an increased response rate and improved recovery of VA. The primary endpoint, the proportion of subacute/dynamic eyes with a	Not a factual inaccuracy, no change required. For reasons outlined in Table 2 and in more detail in the report sections specified in Table 2, the EAG considers there to be a lack of precise effectiveness estimate that was not solely due to the lack of RCT data beyond six months.

		CRB from baseline following 12 months of treatment, compared to the matched external NH cohort, was successfully met. CRB was observed in 42.3% (60/142) of treated eyes. At 24 months, this was maintained, at 52.9% (64/121).(2) The results from the EAP and LEROS demonstrate that there is prolonged clinical benefit in idebenone treated patients.	
Section 3.5, Page 84 *"Although improvements in VA observed for idebenone and placebo after a mean time of 30 months (2.5 years) from week 24 of the RHODOS trial, suggested the benefit of 6 months treatment with idebenone may be maintained after treatment is stopped, the lack of intermediate data collection between the end of RHODOS and OFU visit led to uncertainties in the interpretation of results."*	The Company ask for text to be modified as follows: "***~~Although~~*** *Improvements in VA observed for idebenone and placebo after a mean time of 30 months (2.5 years) from week 24 of the RHODOS trial, suggested the benefit of 6 months treatment with idebenone* ***~~may be~~ is*** *maintained after treatment is stopped****. ~~,~~ ~~the lack of intermediate data collection between the end of RHODOS and OFU visit led to uncertainties in the interpretation of results~~****."*	The Company would like to highlight that RHODOS-OFU was an off-treatment, observational, single-visit, follow up study which examined change in VA of patients who had previously participated in RHODOS and compared current VA with that observed at baseline and after 24 weeks of treatment in RHODOS. The median time that had elapsed between Week 24 of RHODOS and the RHODOS-OFU was 30 months. The study aimed to assess whether any improvement in visual acuity achieved during RHODOS had been maintained and to	The EAG thanks the company for highlighting this and has updated the text on Page 84 to reflect the benefit **'is'** maintained. However, the EAG's concern over the interpretation of results due the lack of intermediate data remains.

		determine the natural course of disease in patients since leaving RHODOS. This clarification in study design and objective was designed to mitigate any uncertainty in the interpretation of the results. In terms of maintenance of treatment benefit, best VA at the RHODOS-OFU visit was slightly worse than at baseline in patients in the placebo group (mean change in logMAR +0.039, corresponding to a worsening of one letter) whereas best VA improved in the idebenone group (mean change in logMAR -0.134, corresponding to an improvement of six letters). The benefit of idebenone was maintained in this off-medication period with a difference of logMAR −0.173 (8 letters); p=0.0845 between treatment groups from baseline in RHODOS to RHODOS-OFU favouring idebenone.(3) The Company would like to highlight that not only did the RHODOS-OFU study show that the treatment effect was	

		maintained in the previously treated idebenone group, but best VA improved by +4 letters from Week 24, highlighting the benefit of idebenone in this off-medication period.	
Section 3.2.3, Page 46, Table 12 "*Since the EAP was restricted to patients with onset of vision loss of less than 12 months, the EAG notes it included a population at an earlier stage of disease progression, than RHODOS, LEROS and the prevalent population in England. Thus, the EAG considers EAP patients to be representative of the incident population of patients with LHON but not prevalent population forming a large part of clinical practice in the UK."* Section 3.2.5, Page 56 *"Contrarily, based on their time since onset of vision loss, the EAG considers the EAP and CaRS patients (within 1 year*	The Company ask for the following text to be added: "*Since the EAP was restricted to patients with onset of vision loss of less than 12 months* ***in the most recently affected eye****, the EAG notes it included a population at an earlier stage of disease progression, than RHODOS, LEROS and the prevalent population in England. Thus, the EAG considers EAP patients to be* ***more*** *representative of the incident population of patients with LHON but not prevalent population forming a large part of clinical practice in the UK."* *"Contrarily, based on their time since onset of vision loss* ***in the most recently affected eye****, the EAG considers the EAP and CaRS patients (within 1 year for >90% of patients) to be representative of LHON patients in the acute and dynamic phase of the disease but not of the chronic phase."*	The Company would like to clarify that the EAP inclusion criteria did not restrict patients based on time since disease onset, but time since onset in the most recently affected eye. Hence, a patient may have had symptomatic LHON for greater than one year in the first eye, but less than one year in the second eye. Furthermore, the baseline demographics of the LEROS trial highlight that 56% patients had disease onset in the second eye of less than one year, with overall mean time since first symptom onset being 18.4 months (1.5 years) across the ITT population.(2) Similarly, in the RHODOS trial, 35.3% of patients had onset of symptoms (in the first eye) of less than one year, and the mean time since onset of vision loss was 23.1	Section 3.2.3, Page 46 The EAG thanks the company for highlighting this and has updated the text on Page 46. The text on Page 56 has not been updated as the EAG also considered data on the onset of vision loss in the first eye available from the EAP CSR (mean/median time since onset in the 1st affected eye at Baseline of 6.2/5 months in the efficacy population and 10.3/5.4 months in the safety population), to confirm if patients could also be representative of people in the chronic phase.

for >90% of patients) to be representative of LHON patients in the acute and dynamic phase of the disease but not of the chronic phase." Section 4.2.4, Page 94 *"Only patients with symptom onset for less than one year were included in the EAP study, while patients with symptom onset of less than five years were included in the LEROS study, which was the same inclusion criteria for RHODOS."* The EAP was restricted only to patients with an onset of less than 12 months in their most recently affected eye, not time since disease onset. Additionally, while the inclusion criteria for LEROS was onset of symptoms less than five years, the majority of patients did have symptom onset of less than one year in the second eye.	*"Only patients with symptom onset for less than one year**, in the most recently affected eye,** were included in the EAP study, while patients with symptom onset of less than five years were included in the LEROS study, which was the same inclusion criteria for RHODOS. **However, we recognise that the majority of patients in the LEROS trial (109/195 [56%]) did have a second eye symptom onset of less than one year."***	months in the ITT population.(4) The Company would like to highlight that the disparity in time since disease onset between the three studies (RHODOS, LEROS and EAP) is not as large as the EAG infer in their report..	The EAG thanks the company for clarifying the inclusion criteria was specific to the most recently affected eye, and has updated the report accordingly.

Section 3.2.3, Page 49 *"Thus, the EAG has concerns over the company's choice of the EAP as the preferred source of log-term effectiveness in the economic model as despite the overall length of follow-up for the EAP being longer, the availability of data was considerably lower."* Section 3.3, Page 58 *"Also, the number of patients on treatment >24 months was low (e.g. N=42; 48.3% at 24 months) in the efficacy population, and the number on treatment at 24 months was substantially reduced to nearly half by 36 months (N=23; 26%) with only 12 patients still receiving treatment at month 42."* The availability of outcome data at 24 months was 48.3% in the EAP and 63.7% in LEROS. Whilst there is a difference between the two studies, 'considerable' is a strong term to describe this. Additionally, the Company	The Company ask for the following text to be modified as follows: *"Thus, the EAG has concerns over the company's choice of the EAP as the preferred source of lo**n**g-term effectiveness in the economic model as despite the overall length of follow-up for the EAP being longer, the availability of data was **~~considerably~~** lower."* *"Also, the number of patients on treatment >24 months was **~~low~~ moderate** (e.g. N=42; 48.3% at 24 months) in the efficacy population, and the number on treatment at 24 months was substantially reduced to nearly half by 36 months (N=23; 26%) with only 12 patients still receiving treatment at month 42."*	The Company acknowledges that the outcome data at 24 months is reduced in the EAP compared to the LEROS trial. However, it is important to note that in the LEROS trial there were no patients with data beyond 24 months, but there were 42 patients in the EAP with data beyond 24 months. This is to be expected as patients have likely responses and plateaued by 24 months, therefore no longer need treatment. These additional patients, with long term follow up beyond 24 months, have been captured in the Company's base case model. The use of EAP data in the economic model was validated by clinical expert opinion who confirmed that the health state predictions based on the RHODOS trial and EAP were sufficient to consider that VA would remain stable following cessation of idebenone after three years of treatment. (5)	Section 3.2.3, Page 49 Not a factual inaccuracy, no change required. The EAG considers the difference in the proportion of patients with data available from the LEROS ITT and the EAP efficacy population at 24 months to be considerable (63.7% vs 48.3%). The EAG thanks the company for highlighting this and has updated the text on Page 58.

considers a follow up rate of 48.3 to be moderate, not low.			
Section 3.4.4, Page 81-82 *"This provides data on the long-term outcomes of people treated with idebenone compared to SoC for a duration of 6 months only, up to Week 132."* Section 3.4.4, Page 83 *"The RHODOS OFU visit, providing data on the Week 132 outcomes of patients treated with idebenone or SoC for 6 months, followed by SoC up to Week 132;"*	The Company ask for text to be modified to: *"This provides data on the long-term outcomes of people **previously** treated with idebenone **(for 6 months)** compared to SoC for a duration of 6 months only, up to Week 132."* *"The RHODOS OFU visit, providing data on the Week 132 outcomes of patients **previously** treated with idebenone or SoC for 6 months, followed by SoC **for both treatment arms** up to Week 132;"*	The Company would like to clarify that no patients in the RHODOS-OFU study were on idebenone treatment. The RHODOS-OFU study was a long-term follow-up study, conducted to determine whether the benefits of idebenone observed in the six-month randomised period in the RHODOS trial were maintained following discontinuation of treatment.	The EAG thanks the company for highlighting this and has updated the text on Page 81 and Page 83 but notes that there were five patients who reported use of idebenone during the RHODOS-OFU follow-up.
Section 4.2.4, Page 95 *"However, after 6 months, the LEROS change in logMAR is less volatile compared to the EAP, possibly due to more patient observations being available in the EAP, and tracks more closely to the RHODOS-OFU study results. The EAP logMAR change from baseline is greater than LEROS and RHODOS-OFU at*	The Company ask for the following text to be removed: *"However, after 6 months, the LEROS change in logMAR is less volatile compared to the EAP, possibly due to more patient observations being available in the EAP**. ~~and tracks more closely to the RHODOS-OFU study results~~**. The EAP logMAR change from baseline is greater than LEROS **~~and RHODOS-OFU at 36 months (from when logMAR is assumed to be fixed),~~** but the LEROS*	The Company would like to clarify that RHODOS-OFU is an off-medication study (no patients in the RHODOS-OFU study were on idebenone treatment) and therefore on-treatment idebenone efficacy results from LEROS and EAP should not be compared to RHODOS-OFU. Additionally, LEROS data are not available beyond 24 months, and therefore a comparison of EAP	The EAG thanks the company for their proposed amendment and has updated the report to more accurately define the limitations of the comparisons.

36 months (from when logMAR is assumed to be fixed), but the LEROS natural history matched analysis identified a comparable logMAR change after 2 years"	*natural history matched analysis identified a comparable logMAR change after 2 years*"	and LEROS at 36 months is not plausible. It is expected that logMAR change from baseline will be greater in EAP than in LEROS due to the longer duration of idebenone treatment, and will also be greater than RHODOS-OFU which reflects patients who were treated with idebenone for 6 months only and then followed by SoC after 6 months	
Section 4.2.4, Page 101 *"All idebenone patients in the model were assumed to experience treatment effects, with no patients experiencing no benefit of treatment. Patients who discontinued idebenone in the model were assumed to continue experiencing idebenone treatment effects and not SoC treatment effects."*	The Company ask for the following text to be added: *"All idebenone patients in the model were assumed to experience treatment effects,* ***in line with RHODOS-OFU,*** *with no patients experiencing no benefit of treatment. Patients who discontinued idebenone in the model were assumed to continue experiencing idebenone treatment effects and not SoC treatment effects,* ***in line with RHODOS-OFU****."*	The Company would like to add justification for the assumption on patient discontinuation. In the RHODOS-OFU study, patients previously treated idebenone for 6 months maintained treatment benefit at time of last visit with best VA improving by +4 letters since Week 24 in RHODOS.	Not a factual inaccuracy, no change required. The company considers that the treatment benefit was maintained, however, SoC patients were recovering at a similar rate to idebenone patients. Therefore, the EAG considers that it may be inappropriate to assume recovery was due to the idebenone treatment effect.
Section 4.2.4, Page 102 *"The EAG notes that as the 4% patient treatment*	The Company ask for the following text to be added:	The Company acknowledge that 12 patients in the EAP discontinued, however not all 12	Not a factual inaccuracy, no change required.

discontinuation was made in addition to the patients already discontinuing treatment within treatment costs, treatment costs in the scenario are likely underestimated as patient treatment discontinuation is potentially double counted. Similarly given that 12 of 111 EAP patients discontinued treatment due to a lack of efficacy, the EAG considers the proportion of patients who discontinue treatment in the scenario should be 10.8%."	"*The EAG notes that as the 4% patient treatment discontinuation was made in addition to the patients already discontinuing treatment within treatment costs, treatment costs in the scenario are likely underestimated as patient treatment discontinuation is potentially double counted. Similarly given that ~~**12**~~ 4 of 111 EAP patients discontinued treatment due to a lack of efficacy, the EAG considers the proportion of patients who discontinue treatment in the scenario should be **3.6**%."*	discontinued due to a lack of efficacy. As captured in response to B8 in the clarification questions, only 4 of the patients who discontinued experienced a lack of efficacy (lack of drug effect [n=1], drug effect incomplete [n=1] and drug ineffective [n=2] as per Table 13.2.2 in the EAP CSR).(6) The Company ask that this scenario be updated in the EAG report to reflect a discontinuation scenario specific to treatment efficacy, and not all-cause discontinuation	The EAG notes that as Table 13.2.2 does not exist in the EAP CSR, nor does Section 13.2.2, the company may instead refer to Table 19 in Section 12.2.2. which describes the analysis of adverse events which includes the four patients as described by the company. The EAG notes that the data used to inform the table was only collected for the AE reporting period (01/07/17 to 30/06/18). A period of approximately one year compared to the three-year EAP study. The EAG notes that in Section 11.5 Treatment Discontinuation, it is clearly described that 12 patients discontinued treatment due to a lack of efficacy over the course of the EAP study.

Issue 2 SoC treatment effect

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.1, Page 14, Table 1: *"The model fails to accurately replicate the SoC treatment effects as measured in studies and clinical trials, with the company failing to derive a treatment effect using all appropriate available data."* Section 4.2.4, Page 98 *"The company did not conduct the requested scenarios, stating that the previously conducted scenario used all available CaRS patient data. Additionally, the natural history matched controlled comparators could not be used due to the matching algorithm being performed de novo at each time point"*	The Company ask for text to be modified to: "*The model ~~fails to accurately replicate the~~* ***is limited in replicating*** *SoC treatment effects as measured in studies and clinical trials, ~~with the company failing to derive a treatment effect using all appropriate available data~~* ***due to the limited number of appropriate observations available to derive a treatment effect****."* *"The company did not conduct the requested scenarios, stating that the previously conducted scenario used all available* ***and useable*** *CaRS patient data. Additionally, the natural history matched controlled comparators could not be used due to the matching algorithm being performed de novo at each time point."*	The Company would like to highlight that all appropriate and available data were used to inform treatment effect scenarios requested by the EAG. The Company believe the EAG may have misinterpreted how the CaRS patient data is used to calculate a patient count. As previously described as part of the Company's response to the clarification questions, a patient must have two consecutive observations within two consecutive 3-month cycle windows in order to inform a patient count. Given that the CaRS patient data is part of natural history database of an ultra-rare disease, the data are extremely limited, with no regular or scheduled follow-up visits. Furthermore, it is likely that patients see no advantage or motivation to attend regular assessments when their VA has no improvement and therefore	Not a factual inaccuracy, no change required. It is the company's opinion that the observations are not usable and inappropriate given the consecutive observations inclusion criteria set out by the company. As suggested in the EAG report, alternative methods could have been explored and used that made the best use of all the available data in order to provide a more robust treatment effect.

		will just stop attending. The Company acknowledge that this is a key limitation within the CaRS dataset for informing 3-monthly transition probabilities, however, this is seen frequently in ultra-rare diseases. Therefore, the Company do not think it is accurate to state that not all appropriate data was used to derive a treatment effect.	
Section 1.3, Table 2, Page 17: "*The EAG notes there were limitations to the PSM analysis and the EAG is mostly concerned that only a limited amount of CaRS follow-up data were included in the analyses by choosing to only analyse a single visit pair, rather than all available data, for SoC patients.*"	The Company ask for the text to be modified to: "*The EAG notes there were limitations to the PSM analysis and the EAG is mostly concerned that only a limited amount of CaRS follow-up data were included in the analyses by choosing to* ***~~only~~*** *analyse a single visit pair****~~, rather than all available data,~~*** *for SoC patients.*"	The Company have conducted the PSM analyses based on similarities between baseline characteristics in the LEROS and CaRS-I and CaRS-II studies. However, as previously mentioned, as the CaRS-I and CaRS-II datasets are part of a natural history study, they lack a defined 'baseline' since there are no interventions initiating a study period and follow-up visits are not scheduled at regular intervals post- onset of symptoms. Given these limitations and considering that one of the matching characteristics includes VA at 'baseline'	Not a factual inaccuracy. No change required.

		alongside time since symptom onset, the Company had reservations about applying the first visit at ‘baseline’ in the PSM analyses for the CaRS-I and CaRS-II data. This approach could potentially result in the absence of comparable follow-up data at 12 or 24 months within a specified 3-month window. For instance, if a patient's follow-up occurs at 3-months and then 16 months, assessing patients from ‘baseline’ for the 12-month endpoint would exclude these two datapoints. However, if we consider the 3-months follow-up as ‘baseline’ and the follow-up at 16 months, this essentially spans 13 months from the 'baseline' and allows the data to be included in the analyses. Therefore, the Company strongly consider that the PSM analyses conducted as part of the clarification questions is the most appropriate method for utilising as much available data and overcoming the challenges	

		associated with natural history studies in an ultra-are disease.	
Section 4.2.4, Page 98 *"Lastly, the company did not conduct a scenario using the RHODOS-OFU study as the company considered the scenario inappropriate."*	The Company ask for text to be modified to ensure that the text is balanced as follows: *"Lastly, the company did not conduct a scenario using the RHODOS-OFU study as the company considered the scenario inappropriate* ***as this would inform only one transition between month 6 and month 30 for a small subset of SoC patients (in RHODOS-OFU a single visit per patient was conducted between month 6 and month 30)."***	As described in the Company's response to the clarification questions, the Company did not conduct a scenario using the RHODOS-OFU study as the study would only inform one transition probability between month 6 and month 30 which was not considered appropriate or an accurate method to capture long-term treatment effect in the SoC arm. The Company would also like to highlight that patients are unblinded at week 24 of the RHODOS trial, and patients on placebo whose VA had not improved or worsened as they reached nadir, would likely drop out of the study.	Not a factual inaccuracy, no change required.
Section 4.2.4, Page 99: "*Given that the RHODOS-OFU study showed a maintained difference in change in logMAR from the end of RHODOS (6 months) to the end of RHODOS-OFU (30*	The Company ask for the text to be modified as follows: "***~~Given that the RHODOS-OFU study~~ Figure 15 in the CS*** *showed a maintained difference in change in logMAR from the end of RHODOS (6 months) to the end of RHODOS-OFU (30 months), between*	The Company would like to highlight that due to the length of the RHODOS trial being 6 months, Figure 15 in the CS does not capture the VA improvement following on from nadir, despite the start of treatment. VA in an individual	Not a factual inaccuracy, no change required.

months), between idebenone and SoC patients (Figure 15 in the CS), the scenario applied the idebenone transition probabilities from LEROS to SoC patients after RHODOS (see Section 6.3).”	*idebenone and SoC patients.* ***However, the EAG acknowledge that this figure does not account for an improvement in VA following nadir and a treatment duration of at least 18–24 months is needed to maximize the probability of CRR from nadir. Nevertheless,*** *the scenario* ***conservatively*** *applied the idebenone transition probabilities from LEROS to SoC patients after RHODOS (see Section 6.3****), ultimately assuming that patients experience no treatment benefit past 6 months.***	eye reaches its lowest point, nadir, in the subacute phase. Learnings from the initial RHODOS trial showed that treatment duration of at least 18–24 months is needed to maximize the probability of CRR because a certain degree of transient deterioration to a nadir may occur despite therapy initiation and continued treatment after an initial CRR provides further benefit. In RHODOS, 34% of patients had already recovered from nadir by week 24 in the idebenone arm, however, in the EAP study, 46% of patients had recovered from nadir at the last observation. This suggests that patients receiving idebenone would be expected to experience an additional clinical benefit if they continued treatment that may not be captured in the 6 months of RHODOS or Figure 15 of the CS. Furthermore, as patients in the RHODOS trial all discontinue treatment at 6 months, the one-off observation recorded as part of RHODOS-OFU is from patients not on	

		treatment. It is therefore inappropriate to assume that there is a maintained difference in change of logMAR between the idebenone and SoC treatment arms from the end of RHODOS at 6 months to the one observation visit of RHODOS-OFU at 30 months as this disregards the natural progression of LHON and the long-term impact of idebenone (beyond the 6 months of RHODOS).	
Section 4.2.4, Page 99 "*As seen in **Error! Reference source not found.**, SoC patient mean change in logMAR under the LEROS transition probabilities scenario aligns more closely to the RHODOS-OFU results compared to the company base case over time."*	The Company ask for text to be modified as follows: "*As seen in **Error! Reference source not found.**, SoC patient mean change in logMAR under the LEROS transition probabilities scenario aligns more closely to **the one observational visit in** RHODOS-OFU ~~**results**~~ compared to the company base case over time."*	The Company wish to highlight to the EAG the difference between the RHODOS-OFU and LEROS studies. RHODOS-OFU is a single observational visit at a median of 30 months after the initiation of treatment in RHODOS RCT. In LEROS, data were collected during six observations post six months. This is important to capture if the EAG wish to compare a single SoC observation to the results of the idebenone arm in the LEROS trial.	Not a factual inaccuracy, no change required.

Section 4.2.4, Page 99 *"The EAG, therefore, includes applying the LEROS treatment effects to SoC patients after the RHODOS treatment effects in its preferred assumptions but caveats that this assumption may be conservative."*	The Company ask for text to be modified as follows: "*The EAG, therefore, includes applying the LEROS treatment effects to SoC patients after the RHODOS treatment effects in its preferred assumptions but caveats that this assumption may be* ***substantially*** *conservative* ***as this now assumes there is no difference in treatment effects between the treatment arms post six months****."*	The Company ask for improved clarity in the text here to ensure the EAGs assumption cannot be misinterpreted. The company would like to highlight that it is clinically implausible to assume that SoC patients would experience the same treatment effect as idebenone treated patients from 6 months onwards. Long term studies (EAP and LEROS) have demonstrated that idebenone can prevent further vision loss and can promote recovery of vision past 6 months. As highlighted in the above issue, 34% of patients in RHODOS had recovered from nadir by month 6 in the idebenone arm, however this increased to 46% of patients in the last observation of the EAP study. Furthermore, in the EAP study, 50% of patients who had a BCVA at baseline of logMAR <1.0 in at least one eye experience a CRS. For patients with CRS, the mean BCVA improved from logMAR 0.47 at baseline to logMAR 0.29 at the	Not a factual inaccuracy, no change required. The EAG notes that the company's LEROS natural history matched analysis and the RHODOS-OFU study (caveating that idebenone patients were not treated for as long), suggest similar treatment effects between idebenone and SoC.

		last visit, corresponding to 9 letter on the ETDRS chart.(6,7) As described above, the clinical course of LHON demonstrates that patients will reach nadir in the subacute phase of the disease, which plateaus at around 1 year after onset. This aligns with RHODOS OFU where best VA at 30 months was actually slightly worse than at baseline in the placebo group of RHODOS (mean change in logMAR +0.039). Choosing to apply the assumption that there is no difference in treatment effect in idebenone patients compared to SoC patients after 6 months based on one visit in an observational follow-up study with a pool of 19 patients, all who had discontinued treatment after 6 months, compared to using CaRS or even LOCF of RHODOS SoC creates significant uncertainty in the modelling. This is echoed by the EAG in their argument for using LEROS over EAP “due to the limited number of patient	

		observations, the transition probabilities are highly uncertain and have far reaching consequences" (*Page 94, ID547 Idebenone EAG report 26012024*).	

Issue 3 Cost-effectiveness results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.4, Table 7 (line 5, column 4), Page 20: "*81,571 (+62,813)"*	The Company propose that the following ICER be amended to: "***59,061 (+40,303)*"**	The independent ICER for the scenario using the LEROS transition probabilities to SoC patients after RHODOS, using the EAGs preferred model structure, is £59,061. The ICER previously stated is the ICER for the scenario using the EAP transition probabilities to SoC patients after RHODOS.	The EAG thanks the company for identifying this inaccuracy and has updated the report accordingly.
Section 6.4, Table 36 (row 5, column 3), Page 126: "*81,571*"	The Company propose that the following ICER be amended to: **"*59,061*"**		
Section 5.2.2, Table 34, page 122:	The Company propose that a footnote be added to Table 34 that states:	Further clarification is needed to distinguish both sets of scenario ICERs.	

	"***Scenarios 1-7 were provided as part of the company submission dossier and were conducted probabilistically based on the Company's base case ICER at submission. Scenarios B1-B21 were provided as part of the clarification question stage and were conducted deterministically based on the Company's updated base case ICER.***"		
Section 5.2.2, Table 34 (row 13, column 5 and column 7), page 122: Incremental costs: "[redacted]" ICER (£): "*17,489 – 21,074*"	Please amend the text to state: Incremental costs: "[redacted]" ICER (£): "***19,107 – 29,407***"	As reported in Table 26 of the Company's clarification question response submitted 28th November 2023 ("*ID547 idebenone clarification letter to PM for company CON_Responses_28Nov23 _Submitted*"), the scenario results using the EAGs proposed health states with the alternative HRQoL sources range from £19,107 – £29,407, which an incremental cost £[redacted].	

Issue 4 HRQoL in LHON

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6, Page 105: *"The EAG notes that none of the utility values sourced by the company from the literature use directly reported EQ-5D-3L as preferred in the NICE Reference Case"*	The Company ask for text to be modified as follows: *"The EAG notes that none of the utility values sourced by the company from the literature use directly reported EQ-5D-3L as preferred in the NICE Reference Case.* ***The EAG do recognize that EQ-5D-3L has been reported as unsuitable for measuring HRQoL in eye conditions, as described in DSU TSD 8 and literature. Alternative measures of HRQoL were also accepted and preferred by NICE in other HTAs in eye conditions, such as HST11, TA298, TA274, TA283 and TA294."***	The Company strongly consider that the use of EQ-5D-3L is inappropriate for measuring HRQoL in eye conditions. NICE guidelines (DSU TSD 8) state that evidence suggests that EQ-5D is not appropriate for assessing the impact of forms of visual impairment.(8) Furthermore, literature has already shown that EQ-5D has poor convergence validity when used in visual disorders and that the EQ-5D index shows poor performance at detecting vision impairment.(9,10) Additionally, the use of alternative measures of HRQoL were also implemented in numerous other similar HTAs in eye conditions (HST11, TA298, TA274, TA283 and TA294). Whilst the Company recognise that the NICE preferred HRQoL measure is EQ-5D-3L, the NICE manual (2022) (Figure 4.1)	Not a factual inaccuracy, no change required. The EAG would like to clarify that the DSU TSD 8 guidance outlines that EQ-5D-3L may be inappropriate for specific forms of visual impairment as *"psychometrics literature often uses clinical measures such as visual acuity, respiratory function or symptoms of schizophrenia that may have only a weak relationship to HRQL in any case".*

		states that alternative methods should be used when EQ-5D-3L is not appropriate. The Company acknowledge that the utility values elicited in Lawrence at al. 2023b may have been developed for patients with LHON, however, given the above, EQ-5D is not an acceptable measure for this HTA.	
Section 4.2.6.4, Page 108 "*The EAG notes that although the same disutility values were applied in HST11 to reflect the impact on caregivers for caring for a family member experiencing blindness, the committee concluded that these values should only be applied to carers of children and not adults and therefore the exclusion of a carer disutility for adult patients was used for decision making. Although the EAG recognises that patients experiencing blindness will require additional assistance from a caregiver, based on the available evidence, the disutility impact on caregivers*	The Company ask that the EAG modify the text as follows: "*The EAG notes that although the same disutility values were applied in HST11 to reflect the impact on caregivers for caring for a family member experiencing blindness, the committee concluded that these values should only be applied to carers of children and not adults and therefore the exclusion of a carer disutility for adult patients was used for decision making. Although the EAG recognises that patients experiencing blindness will require additional assistance from a caregiver, **~~based on the available evidence, the disutility impact on caregivers is uncertain.~~** The EAG preferred analysis applies **~~no~~** caregiver disutility in the base-case, with a scenario*	The Company do not think it is reasonable to assume that only children who experience blindness would require a caregiver. The majority of LHON patients are diagnosed at a working age, and the blindness occurs rapidly, which has a significant impact on patients ability to work and perform daily activities. Support in the form of informal care from family members is absolutely fundamental to patients, particularly in the beginning stages of their vision loss whilst the patient is adjusting to this huge life change. This is demonstrated in the study by Williams et al. (2023) which described the burden of LHON to	Not a factual inaccuracy, no change required.

is uncertain. The EAG preferred analysis applies no caregiver disutility in the base-case, with a scenario analysis provided to explore the impact of its inclusion."	*analysis provided to explore the impact of its* ***~~inclusion~~ exclusion****.*"	caregivers.(11) The study included N=9 caregivers and family members who cared for adult patients with LHON aged 17-73 years old (mean age of 32 years). The study suggests a substantial burden for many caregivers with impacts reported across numerous aspects of life; emotional, daily life, social life and relationships, work and career, financial and wider family. The study reports that caregivers "*discussed how their daily routine and activities had changed to accommodate their care tasks*" and "*worry about the future was a prominent theme across interviews*". The study also reports a substantial emotional burden and that "*Mothers discussed immense feelings of guilt for passing on a gene that caused their child's vision loss*" and the "*profound emotional impact of caring for someone with LHON had knock on effects on other areas of life*". Given the above, the Company consider including caregiver disutility reasonable and ask that the EAG reconsider excluding a	

		caregiver disutility in the base-case CEA.	

Issue 5 Clarification of the persistence data used

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 6.3, Table 35, pages 124-125	The Company propose that a footnote be added to Table 35 that states: "***Scenario 1 applied the RHODOS/EAP persistence data alongside the LEROS transition probabilities.***"	In the Company's scenario using LEROS transition probabilities, RHODOS/LEROS persistence data was applied to idebenone costs. In the EAGs preferred scenario, RHODOS/EAP persistence is applied to the idebenone costs even when using LEROS transition probabilities. It is important to define this change in assumption within the EAGs results. Furthermore, the Company request that the EAG acknowledge the overly conservative assumption of applying RHODOS/EAP persistence data with the RHODOS/LEROS clinical effectiveness data. The Company strongly consider that the inconsistent use of	In Scenario 1 of Table 35 and the third assumption in Table 36, only the LEROS transition probabilities were applied to SoC patients. Therefore, no additional foot note is required. With respect to the second assumption in Table 36. The EAG thanks the company for the proposed amendment and has added a footnote accordingly. The EAG considers that it would be inappropriate to use the LEROS discontinuation data
Section 6.4, page 125: *"Using the LEROS study to derive the idebenone long-term treatment effects;"*	The Company propose that the following text be amended to: "*Using the LEROS study data* ***with the RHODOS/EAP persistence data applied*** *to derive the idebenone long-term treatment effects;*"		
Table 36 (row 4 and row 5, column 3), page 12:	The Company propose that a footnote be added to the ICERs in row 4 and row 5, column 3 of Table 36 followed by a footnote that states: **"***The scenarios using LEROS data are with the RHODOS/EAP persistence data applied."**		

		treatment effect data with the treatment discontinuation data to be inappropriate. The EAG are assuming that there are no treatment benefits to patients past 24 months, despite patients still accruing treatment costs which is considerably biased against idebenone. As demonstrated in the model, the RHODOS/EAP persistence data still estimates that [redacted]% of patients are accruing treatment costs at 24 months with no treatment benefit if LEROS clinical effectiveness is used. Furthermore, the pattern of treatment discontinuation will not align with the pattern demonstrated in the treatment effects, which the EAG have already highlighted as an issue in the Company's base case assumptions (Section 4.2.4.5.1). For example, the RHODOS/LEROS transition probabilities may capture a patient who has discontinued treatment with idebenone or has been lost to follow-up, however, could still be accruing treatment costs in the model through the	given the limited study duration (only two years) compared to how treatments would be prescribed in clinical practice (three years and potentially more if VA has still not stabilised). which the EAG considers to be better represented by the EAP discontinuation data.

		use of the RHODOS/EAP persistence data. Therefore, the Company strongly consider that the EAG's current scenario is inappropriate and that the RHODOS/LEROS persistence data should be applied when using the RHODOS/LEROS transition probabilities.	

Issue 6 Systematic literature review

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.1, Page 37: *"The EAG considered all other eligibility criteria of the SLR to appropriately reflect the final scope as issued by NICE, although non-interventional studies were excluded from the real-world evidence SLR"*	The Company ask for the following text to be added: *"The EAG considered all other eligibility criteria of the SLR to appropriately reflect the final scope as issued by NICE, although non-interventional studies,* ***where unclear whether the population was treated or not****, were excluded from the real-world evidence SLR"*	The Company asks the EAG to add the conditions to which non-interventional studies were excluded for improved clarity. These conditions were provided in response to A5 in clarification questions. The studies were excluded due to: • Studies reported anatomical, physiological, genetic, or biochemical features of the disease • Studies did not make any reference to treatment	The EAG thanks the company for highlighting this. In line with the Company response to Clarification Question A4 and the EAG's main concern about studies of non-pharmacological interventions not being included in the SLR, the EAG has updated the text to read: "The EAG considered all other eligibility criteria of the SLR to appropriately reflect the final scope as

		(i.e., it is unclear whether the population was treated or not) • Studies reported epidemiology of LHON (incidence/ prevalence)	issued by NICE, although studies of no pharmacological intervention (i.e., current SoC) were excluded from the real-world evidence SLR."

Issue 7 Reporting of the clinical trials

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3, Table 3 (row 2), page 18: "*The EAG notes that the clinical trials were not powered to detect subgroup effects with subgroup sample sizes being too small to support meaningful conclusions about a difference in the magnitude of treatment effect between different subgroups of patients."*	The Company propose for the following text to be added: "*The EAG notes that the clinical trials were not powered to detect subgroup effects with subgroup sample sizes being too small to support meaningful conclusions about a difference in the magnitude of treatment effect between different subgroups of patients.* ***However, the EAG recognise that LHON is an ultra-rare disease and therefore patients numbers are already low.****"*	The Company would like to highlight that LHON is an ultra-rare disease with a very small patient population worldwide. Whilst the Company recognise that clinical trials including a larger patient population may be useful in addressing the data limitations, it is not feasible given the rarity of the condition and the worldwide prevalence of some of the subgroup populations. Small clinical trial population is a common challenge faced in rare-diseases, and that challenge is	Not a factual inaccuracy. No change required. However, text corresponding to the suggestion below has been amended to acknowledge the rarity of LHON. See response below.

Section 1.3, Table 3 (row5), page 18: *"Future trials including larger datasets, sufficiently powered to detect subgroup effects would be useful to resolve uncertainties regarding treatment effectiveness."*	The Company propose the text be amended to read: "***Whilst** future trials including larger datasets, sufficiently powered to detect subgroups effects**, may be** useful to resolve uncertainties regarding treatment effectiveness**, the EAG recognise that LHON is an ultra-rare disease and small patient numbers in clinical trials is a common challenge.***"	no different in the clinical studies for LHON.	The EAG thanks the company for highlighting this and the text in row 5 has updated to read: "*Future trials including larger datasets, sufficiently powered to detect subgroup effects would be useful to resolve uncertainties regarding treatment effectiveness.* ***However, the EAG recognises that LHON is a rare disease, and this may present a challenge****."*
Section 3.3, Page 57: *"Therefore, the EAG requested that the company provide results from the ITT population."*	The Company ask for the following text to be added: *"Therefore, the EAG requested that the company provide results from the ITT population.* ***The request was fulfilled by the Company."***	The Company ask for text to be modified to ensure that the text is clear that the Company did provide the requested analyses.	The EAG thanks the company and has updated the text on Page 57.
Section 1.1, Table 1 (row 2), page 14: *"3.2.2, 3.2.4, 3.4"*	The Company ask for the following text to be amended to: "~~***3.2.2,***~~ *3.2.4, 3.4*"	The company want to note that the comments related to RHODOS-OFU are not applicable to this statement, as the purpose of RHODOS-OFU was to evaluate the persistence of the effects achieved in the double-blind RHODOS and that	The EAG thanks the company for highlighting this and has updated the text in Table 1 as well as the equivalent text in related Table 2.

		patients were off-treatment in the RHODOS-OFU study.	
Section 1.3, Table 2 (row 2), page 17: "*resulting in an estimate at high risk of bias due to imbalances in prognostic factors between patients from the data sources*."	The Company ask for the following text to be amended to: "*resulting in an estimate at* ***~~high~~*** *risk of bias due to imbalances in prognostic factors between patients from the data sources.* ***However, the EAG notes that LHON is an ultra-rare disease and patient populations are already small.****"*	The company would like to highlight that that LHON is an ultra-rare disease with a very small patient population worldwide and therefore there are naturally limitations within the available data. Given the shorter duration of the RHODOS trial but the need to model the clinical effects of patients over a longer period, data for alternative sources were utilised in order to accurately model the disease course and clinical effects of idebenone over time. The two populations from the EAP and CaRS studies were not matched as the populations were already small and creating a smaller sample size would increase the uncertainty in the data.	Not a factual inaccuracy. No change required.

Issue 8 Statistical and modelling methods

Description of problem	Description of proposed amendment	Justification for amendment	
Section 3.4.2, Bullet point 2, Page 77: *"Through PSM, 68 of the 84 available NH patients to be matched to 68 of 125 LEROS ITT patients. The exact method of selecting which visit pair to include for each patient was not clearly reported."*	The Company ask for the following text to be removed: *"Through PSM, 68 of the 84 available NH patients to be matched to 68 of 125 LEROS ITT patients.* ***~~The exact method of selecting which visit pair to include for each patient was not clearly reported."~~***	The Company would like to highlight that the method of selecting patients and visits is clearly described in the response to question A2 in clarification questions (pages 6 and 7). A specific approach was employed at each time point to determine each visit pair. Taking 24 months as an example, all NH patients with pairs of visits showing a 24-month delta within a 3-month window were selected. Subsequently, for each NH patient, the visit pair that most closely matched the mean time since the first symptoms onset, as observed in LEROS patients, was identified and chosen. This methodology aimed to align the NH patient data as closely as possible with the LEROS mean. The final dataset, comprising only one visit per patient, was then utilized for PSM.	The EAG thanks the company for highlighting this, the text has been removed.

Section 4.2.2, Page 90 *"For example, under both probabilistic and deterministic conditions it is impossible for idebenone treated patients to remain in the Hand Movement health state past cycle 10 (2.5 years) in the company's model. The EAG therefore considers that the company model is flawed and potentially inappropriate for decision making as there is insufficient evidence to support the high number of health states in the economic model given the modest differences in HRQoL and functional capabilities between some of the health states according to the EAG's clinical experts. "* Section 4.2.2, Page 90-91: *"The EAG additionally considers that that the reduction in health states also makes the best use of the limited available patient data as it avoids the implausible model transitions exhibited in*	The Company request for the following text to be removed: ***~~"For example, under both probabilistic and deterministic conditions it is impossible for idebenone treated patients to remain in the Hand Movement health state past cycle 10 (2.5 years) in the company's model. The EAG therefore considers that the company model is flawed and potentially inappropriate for decision making as there is insufficient evidence to support the high number of health states in the economic model given the modest differences in HRQoL and functional capabilities between some of the health states according to the EAG's clinical experts. "~~*** *The EAG additionally considers that* ***~~that~~*** *the reduction in health states also makes the best use of the limited available patient data****. ~~as it avoids the implausible model transitions exhibited in the company's base-case model.~~*** ***~~"For example, under both probabilistic and deterministic conditions, idebenone treated patients are unable~~***	The Company would like to clarify that no transition in the CEM is impossible and no restrictions on transitions have been applied. The Company have applied patient transitions as reflective of the EAP data set. Where a transition did not exist for a health state from the data, the Company applied an assumption to the model that all patients would remain in the same health state for that cycle. The Company acknowledge that data is limited given the ultra-rarity of LHON and have explained the need to impute transitions for certain time points. This is a common occurrence when modelling rare diseases and the Company have ensured that the most appropriate clinical data has been utilised and explored the uncertainty through deterministic and probabilistic sensitivity analyses and scenario analyses.	Not a factual inaccuracy. No change required.

the company's base-case model." *Section 4.2.4, Page 94:* "*For example, under both probabilistic and deterministic conditions, idebenone treated patients are unable to move to or remain in the Hand Movement health state past cycle 10 (two and a half years in the model). It's similarly impossible for any idebenone treated patients to be logMAR 0.3 to 0.6 between cycles 8 and 9."*	***~~to move to or remain in the Hand Movement health state past cycle 10 (two and a half years in the model). It's similarly impossible for any idebenone treated patients to be logMAR 0.3 to 0.6 between cycles 8 and 9."~~***		
Section 4.2.4, Page 97 *"The EAG noted that in the company's scenario, transition probabilities from month 6 to 36 were informed using only 169 observations, compared to the 740 observations when using CaRS-I and LOCF. In contrast, the company reported in Table 1 of the*	The Company request for the following text to be removed: "*The EAG noted that in the company's scenario, transition probabilities from month 6 to 36 were informed using only 169 observations, compared to the 740 observations when using CaRS-I and LOCF. In contrast, the company reported in Table 1 of the supplementary clarification response that 944 appropriate*	The Company would like to highlight that while 944 observations were available to calculate the pooled transition probabilities, not all were usable. Only patients which had consecutive observations were included, which narrowed the number of usable observations.	Not a factual inaccuracy. No change required. It is the company's opinion that the observations are not usable and inappropriate given the consecutive observations inclusion criteria set out by the company. As suggested in the EAG

supplementary clarification response that 944 appropriate and usable observations (from the 5,186 observations recorded in the studies) taken from the 385 appropriate patients from CaRS-I and -II are available." Section 4.2.4, Page 97 *"The EAG additionally notes that a more robust treatment effect may be calculated and used in the model should the company have utilised all appropriate and available patient observations from the CaRS studies."*	***~~and usable~~*** *observations (from the 5,186 observations recorded in the studies) taken from the 385 appropriate patients from CaRS-I and -II are available."* *"The EAG additionally notes that a more robust treatment effect may be calculated and used in the model should the company have utilised all* ***~~appropriate and~~*** *available patient observations from the CaRS studies."*		report, alternative methods could have been explored and used that made the best use of all the available data in order to provide a more robust treatment effect.
Section 4.2.4, Page 101 *"As such, the PSA does not account for treatment effectiveness uncertainty for either idebenone or SoC treatment effects. This is a key issue, as the EAG considers the treatment effects to be highly uncertain given the limited patient data and that the NICE Guide to the*	The Company request for the following text to be modified: *"****~~As such, the PSA does not account for treatment effectiveness uncertainty for either idebenone or SoC treatment effects.~~*** *This is a key issue, as the EAG considers the* ***~~treatment effects~~ transition probabilities*** *to be highly uncertain given the limited patient data and that the NICE Guide to the Methods of Technology Appraisal states that PSA results are no longer simply recommended but are a mandatory*	The Company reiterate that due to the ultra-rarity of LHON and the resulting low patient numbers and available data to inform the transition probabilities, including them in the probabilistic sensitivity analyses creates substantial uncertainty in the probabilistic ICER and will not give an accurate representation of the probabilistic ICER for this CEA.	Not a factual inaccuracy. No change required. The joint uncertainty in the estimates of treatment effectiveness, and the other model parameters, is exactly what the probabilistic sensitivity analysis is designed to assess. The company's approach implies that there is no uncertainty in the treatment effectiveness

Methods of Technology Appraisal states that PSA results are no longer simply recommended but are a mandatory requirement for all cost-effectiveness models submitted to NICE." Section 6.5, Paragraph 2, Page 128 *"While the company has attempted to justify the exclusion of treatment effectiveness uncertainty from the sensitivity analysis by suggesting it's inclusion will create substantial uncertainty in the results, the EAG considers this a critical flaw in the development of the model. Investigating the impact of parameter uncertainty on the incremental cost effectiveness ratio (ICER) is a critical step in the evaluation of new health technologies."*	*requirement for all cost-effectiveness models submitted to NICE."* *"While the company has attempted to justify the exclusion of* ***~~treatment effectiveness~~ transition probability*** *uncertainty from the sensitivity analysis by suggesting it's inclusion will create substantial uncertainty in the results, the EAG considers this a critical flaw in the development of the model. Investigating the impact of parameter uncertainty on the incremental cost effectiveness ratio (ICER) is a critical step in the evaluation of new health technologies."*	As previously stated, the Company have instead explored and presented the uncertainty in the transition probabilities through the varying of the baseline distribution in the sensitivity analyses and testing scenarios with alternative clinical sources (RHODOS, EAP, LEROS , CaRS I/CaRS II), all of which produced ICERs below the £30,000 threshold when using the company's model structure and the EAG's preferred model structure (see Table 2 of "*Company's Response_ID547 idebenone EAG supplementary clarification letter 2_v1.0_20Dec23*").	estimates used in the model.

Issue 9 Interpretation of CRR

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.4.2.1, Page 93 *"In evaluation of CRR as a clinically relevant measure, the EAG notes that as CRR is defined as improvement of at least logMAR 0.2 (equal to two lines of readable letters on a logMAR chart) for patients with "on-chart" VA at baseline, or an improvement from "off-chart" VA to at least logMAR 1.6 (equal to one line on-chart) for patients with off-chart VA at baseline, CRR may be achieved with no difference in functional sight or change in HRQoL (patients are still considered vision impaired or unable conduct key autonomous function such as driving). Therefore, CRR may not be a helpful indicator of improved HRQoL as it does not differentiate between sight recovery and functional sight recovery. For example, although 30% of idebenone patients achieved CRR in*	The Company ask for the following text to be removed: ***~~"In evaluation of CRR as a clinically relevant measure, the EAG notes that as CRR is defined as improvement of at least logMAR 0.2 (equal to two lines of readable letters on a logMAR chart) for patients with "on-chart" VA at baseline, or an improvement from "off-chart" VA to at least logMAR 1.6 (equal to one line on-chart) for patients with off-chart VA at baseline, CRR may be achieved with no difference in functional sight or change in HRQoL (patients are still considered vision impaired or unable conduct key autonomous function such as driving). Therefore, CRR may not be a helpful indicator of improved HRQoL as it does not differentiate between sight recovery and functional sight recovery. For example, although 30% of idebenone patients achieved CRR in RHODOS after six months, mean recovery in terms of logMAR was 0.037, the equivalent of 1 letter on a logMAR chart."~~***</u>	The Company ask for text to be removed on the grounds that CRR is a clinically relevant measure which would have immense impact on a patient's functional sight and quality of life. While a patient may still be considered visually impaired, an idebenone patient may be able to stabilise or, recover vision loss. The Company consider the EAG to underestimate the value of a patient stabilising or improving vision when faced with a prognosis of lifelong blindness, when left untreated. When treating patients in the acute phase of LHON whose VA is still declining, patients are more likely to experience stabilisation of vision rather than recovery. This stabilisation in the acute phase can lead to a final VA which is better than if a patient had been allowed to continue to nadir, and then recover.	Not a factual inaccuracy. No change required.

RHODOS after six months, mean recovery in terms of logMAR was 0.037, the equivalent of 1 letter on a logMAR chart."			
Section 3.3.2, Page 65, last paragraph: *"The EAG notes the considerable proportion with CRR in CaRS-I was achieved without receiving treatment and could therefore have been a result of spontaneous recovery."*	Please can the EAG update the text as appropriate to either: *"The EAG notes the considerable proportion with CRR **from baseline** in CaRS-I was achieved without receiving treatment and could therefore have been a result of spontaneous recovery."* *Or* *"The EAG notes the considerable proportion with CRR **from nadir** in CaRS-I was achieved without receiving treatment and could therefore have been a result of spontaneous recovery."*	The Company would like to request clarification on whether this CRR is from baseline or nadir.	The EAG thanks the company for highlighting the inaccuracy and has updated the text to ***from nadir*.**

Issue 10 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2, page 21: *"In chronic LHON, a patient's VA is usually stable, but the*	Please amend the text as follows: *"In chronic LHON, a patient's VA is usually stable, but the EAG's clinical experts noted that some further decline is **possible**."*	Typographical error.	The EAG thanks the company for highlighting this inaccuracy and has

EAG's clinical experts noted that some further decline is posisble."			updated the text accordingly.
Section 2.2.1, Bullet point 2, Page 23: "● *0.3≤ LogMAR ≤1.0: Not sight impaired, unable to drive;*"	Please amend the text as follows: "● *0.3≤ LogMAR **<**1.0: Not sight impaired, unable to drive;*"	Typographical error.	
Section 2.2.1, page 23: *"Do you have any difficulty, even with glasses, reading small print, such as labels on medicine bottles, a telephone book, or food labels?" and "Do you have any difficulty, even with glasses, recognizing people when they are close to you?".*	Please amend the text as follows: *"Do you have any difficulty, even with glasses, reading small print, such as labels on medicine bottles, a telephone book, or food labels?" and "Do you have any difficulty, even with glasses, **recognising** people when they are close to you?".*	Typographical error.	Not a typographical error as the EAG was directly quoting the VF-14 questions from Steinberg *et al.* 1994.

Section 2.2.2, Figure 3, heading, page 25: "*Figure 3. Characteristics assocaited with LHON genotpes m.11778G>A, m.3460G>A and m.14484T>C"*	Please amend the text as follows: "*Figure 3. Characteristics **associated** with LHON **genotypes** m.11778G>A, m.3460G>A and m.14484T>C"*	Typographical error.	The EAG thanks the company for highlighting this inaccuracy and has updated the text accordingly.
Section 2.3, Table 9 (row 6), page 27: "*Brown et al. (1999) demonstrated that a patient's quality of life is attributed more by the better-seeing eye than the worst-seeing eye.[23] The better-seeing eye has a higher predictability and consistency when measuring quality of life compared to the worst-seeing eye.[23] Furthermore, change in best VA was the main secondary endpoint in the RHODOS trial. It was considered to be the endpoint most relevant to clinical practice and the one that best reflects the impact of the disease on a patient, being the closest related to visual function in daily life.[24, 25]*	Please amend the text as follows: "*Brown et al. (1999) demonstrated that a patient's quality of life is attributed more by the better-seeing eye than the worst-seeing eye.[23] The better-seeing eye has a higher predictability and consistency when measuring quality of life compared to the worst-seeing eye.[23] Furthermore, change in best VA was the main secondary endpoint in the RHODOS trial. It was considered to be the endpoint most relevant to clinical practice and the one that best reflects the impact of the disease on a patient, being the closest related to visual function in daily life.[24, 25] Furthermore, during protocol assistance the CHMP agreed with the rational for including this endpoint and that it may be more clinically relevant than the primary endpoint analysis (best recovery of logMAR VA between baseline and Week 24). **~~Brown et al. (1999) demonstrated~~***"	Text repetition.	

Furthermore, during protocol assistance the CHMP agreed with the rational for including this endpoint and that it may be more clinically relevant than the primary endpoint analysis (best recovery of logMAR VA between baseline and Week 24). Brown et al. (1999) demonstrated that a patient's quality of life is attributed more by the better-seeing eye than the worst-seeing eye.[23] The better-seeing eye has a higher predictability and consistency when measuring quality of life compared to the worst-seeing eye.[23] Furthermore, change in best VA was the main secondary endpoint in the RHODOS trial. It was considered to be the endpoint most relevant to clinical practice and the one that best reflects the impact of the disease on a patient, being the closest related to visual function in daily life.[24, 25] Furthermore, during protocol assistance the CHMP agreed with the rational for including this endpoint and that it may be	***~~that a patient's quality of life is attributed more by the better-seeing eye than the worst-seeing eye.[23] The better-seeing eye has a higher predictability and consistency when measuring quality of life compared to the worst-seeing eye.[23] Furthermore, change in best VA was the main secondary endpoint in the RHODOS trial. It was considered to be the endpoint most relevant to clinical practice and the one that best reflects the impact of the disease on a patient, being the closest related to visual function in daily life.[24, 25] Furthermore, during protocol assistance the CHMP agreed with the rational for including this endpoint and that it may be more clinically relevant than the primary endpoint analysis (best recovery of logMAR VA between baseline and Week 24).~~*** *This also aligns with the health technology assessments of idebenone in Wales and Scotland, both of which focused on change in best VA and were granted national reimbursement for patients with LHON.[26, 27]*"		

more clinically relevant than the primary endpoint analysis (best recovery of logMAR VA between baseline and Week 24). *This also aligns with the health technology assessments of idebenone in Wales and Scotland, both of which focused on change in best VA and were granted national reimbursement for patients with LHON.*[26, 27]"			
Section 2.3, Table 9, row 7, page 31: *"See Section 2.3.6 below for further discussion; the results of subgroup analyses from the primary sources of clinical evidence are presented in Section 3.3"*	Please amend the text as follows: *"See Section **2.3.5** below for further discussion; the results of subgroup analyses from the primary sources of clinical evidence are presented in Section 3.3"*	Typographical error.	

Section 2.3, Table 9, abbreviations, page 31: *"Abbreviations: CHMP, Committee for Medica Products for Human Use; CS. Company Submission; EAG, External Assessment Group; HRQoL, Health related quality of life; LHON, Leber's hereditary optic neuropathy; logMAR, logarithm of the minimum angle of resolution; NICE, National Institute for Health and Care Excellence; VA, visual acuity"*	Please amend the text as follows: *"Abbreviations: CHMP, Committee for **Medicinal** Products for Human Use; CS. Company Submission; EAG, External Assessment Group; HRQoL, Health related quality of life; LHON, Leber's hereditary optic neuropathy; logMAR, logarithm of the minimum angle of resolution; NICE, National Institute for Health and Care Excellence; VA, visual acuity"*	Typographical error.	
Section 2.3.1, Page 32: "…*confirmation of either m.11778G>A; m.14484T>C; and m.3460G>A mtDNA mutations at >60% in blood…"*	Please amend the text as follow: "*confirmation of either m.11778G>A; m.14484T>C; **~~and~~ or** m.3460G>A mtDNA mutations at >60% in blood*	Typographical error.	
Section 2.3.1, page 32: "…*included patients aged ≥12 years, whose onset of symptoms dated after 1999 and was 'well documeted' (at least the month pf the onset of symptoms was known for each eye…"*	Please amend the text as follows: "…*included patients aged ≥12 years, whose onset of symptoms dated after 1999 and was 'well **documented**' (at least the month **of** the onset of symptoms was known for each eye…"*	Typographical error.	

Section 2.3.1, page 33: *"The EAG also notes that while the population in the NICE final scope is people with LHON aged 12 years, patients younger than 14 years were excluded in the RHODOS RCT."*	Please amend the text as follows: *"The EAG also notes that while the population in the NICE final scope is people with LHON aged 12 years **and over**, patients younger than 14 years were excluded in the RHODOS RCT."*	Typographical error.	
Section 2.3.2, page 33: "*Idebenone (Raxone®), a short-chain benzoquinone, is antioxidant that as outlined in Table 2 of the CS is thought to re-activate viable-but-inactive retinal ganglion cells (RGCs) in LHON patients by restoring cellular energy (ATP) generation"*	Please amend the text as follows: "*Idebenone (Raxone®), a short-chain benzoquinone, is **an** antioxidant that**,** as outlined in Table 2 of the CS is thought to re-activate viable-but-inactive retinal ganglion cells (RGCs) in LHON patients by restoring cellular energy (ATP) generation"*	Typographical error.	
Section 3.1, Table 10, row 2, bullet point 3, page 38: "*Nine HTA body websites were searched, and are were in Table 8 of Appendix D"*	Please amend the text as follows: "*Nine HTA body websites were searched, and **detailed ~~are were~~** in Table 8 of Appendix D"*	Typographical error.	The EAG thanks the company for highlighting this and has updated the text in Page 38 to reflect these were "presented" in Table 8 of Appendix D.

Section 3.1, Table 10, row 4, page 38: *"The EAG is concerned that non-interventional studies were been excluded from the real-world evidence SLR, but the comparator in the current appraisal is no intervention."*	Please amend the text as follows: *"The EAG is concerned that non-interventional studies were* ***~~been~~*** *excluded from the real-world evidence SLR, but the comparator in the current appraisal is no intervention."*	Typographical error.	The EAG thanks the company for highlighting this inaccuracy and has updated the text accordingly.
Section 3.1,Table 10, abbreviations, page 38: *"NICE, National Institute of Health and Care Excellence"*	Please amend the text as follows: *"NICE, National Institute* ***~~of~~ for*** *Health and Care Excellence"*	Typographical error.	
Section 3.1, page 40: "*While the EAG considered it plausible excluded studies such as Van Everdingen 2022,[32] a retrospective multicentre study of idebenone in the Netherlands, could contain relevant data, the study did not report the individual participant transition probabilities between logMAR states that would be required for inclusion in the economic model."*	Please amend the text as follows: *"While the EAG considered it plausible* ***to ~~excluded~~ exclude*** *studies such as Van Everdingen 2022,[32] a retrospective multicentre study of idebenone in the Netherlands, which could contain relevant data****,*** *the study did not report the individual participant transition probabilities between logMAR states that would be required for inclusion in the economic model."*	Typographical error.	

Section 3.2, page 40: *"Data informing the disease course of LHON under established clinical management was presented up to 6 months from the placebo arm of RHODOS…"*	Please amend the text as follows: *"Data informing the disease course of LHON under established clinical management ~~was~~* ***were*** *presented up to 6 months from the placebo arm of RHODOS…"*	Typographical error.	
Section 3.2.1, Table 11, row 10 – Analysis sets, page 43 "*The ITT population (n=81) included all randomised patients who received at least one dose of the study medication, with three patients prospectively excluded for all VA analyses due to inaccurate recordings in VA measurements either at baseline or visit 4 (week 24)."* *"The mITT population (n=82) was the same as the ITT population, but for VA and colour contrast analyses, one patient randomised to placebo, who was identified as a natural history confounder due to ongoing spontaneous recovery of vision at the time of randomisation was excluded."*	Please amend the text as follows: "*The ITT population (n=****82****) included all randomised patients who received at least one dose of the study medication, with three patients prospectively excluded for all VA analyses due to inaccurate recordings in VA measurements either at baseline or visit* ***5*** *(week 24).*" *"The mITT population (n=****81****) was the same as the ITT population, but for VA and colour contrast analyses, one patient randomised to placebo, who was identified as a natural history confounder due to ongoing spontaneous recovery of vision at the time of randomisation was excluded."*	Typographical error.	

Section 3.2.2, page 44 *"However, there were five patients from the total efficacy population (three from the idebenone group and two from the placebo group) who reported use of idebenone between Week 24 or RHODOS and the RHODOS-OFU single visit (median 30 months, range: 20.9 to 42.5 months)"*	Please amend the text as follows: *"However, there were five patients from the total efficacy population (three from the idebenone group and two from the placebo group) who reported use of idebenone between Week 24 **~~or~~ of** RHODOS and the RHODOS-OFU single visit (median 30 months, range: 20.9 to 42.5 months)"*	Typographical error.	
Section 3.2.2, page 44 *"However, the EAG notes that the number of patients included in the RHODOS-OFU visit was lower than that included in the original RHODOS trial and the proportion of patients from the original sample included in RHODOS-OFU also differed between the idebenone (70.9%) and the SoC (63.3%) groups."*	Please amend the text as follows: *"However, the EAG notes that the number of patients included in the RHODOS-OFU visit was lower than that included in the original RHODOS trial and the proportion of patients from the original sample included in RHODOS-OFU also differed between the idebenone (**73.6**%) and the SoC (**65.5**%) groups."*	Typographical error. The baseline characteristics of patients in the RHODOS-OFU study are located in Table 8 of the CS document.	

Section 3.2.3, Table 12, row 1, page 46: *"Given LEROS was a natural history, controlled study of patients treated with idebenone with no enrolled comparator group, there was no randomisation procedure and blinding, and concealment of allocation were not applicable."*	Please amend the text as follows: *"Given LEROS was a natural history~~,~~ controlled study of patients treated with idebenone with no enrolled comparator group, there was no randomisation procedure and blinding, and concealment of allocation were not applicable."*	Punctuation error.	
Section 3.2.4, page 49 *"CaRS-I (n=373) collected historical case record data from LHON patients (with genetically confirmed diagnosis), from 11 participating clinical centres; no inclusion criteria were specified, and data were collected non-systematically without pre-selection, based on participating clinical centres record-keeping practices."*	Please amend the text as follows: *"CaRS-I (n=**383**) collected historical case record data from LHON patients (with genetically confirmed diagnosis), from 11 participating clinical centres; no **~~inclusion~~ exclusion** criteria were specified, and data were collected **~~non-systematically~~** without pre-selection, based on participating clinical centres record-keeping practices."*	Typographical error.	

Section 3.2.4, page 50 *"In the CSR, it is noted that the studies were collecting historical case records from participating centres where all available VA information..."*	Please amend the text as follows: *"In the CSR of **CaRS-I**, it is noted that the studies were collecting historical case records from participating centres where all available VA information..."*	Proposed to add the name of the study.	
Section 3.2.5, page 57: *"…mutation compared to RHODOS, the EAP and the LEROS trial. EAG clinical experts have emphasised this mutation has worse prognosis, thus the EAG is concerned about the impact of this difference on the results and conclusions drawn about treatment…"*	Please amend the text as follows: *"…mutation compared to RHODOS, the EAP and the LEROS trial. EAG clinical experts have emphasised this mutation has ~~**worse**~~ **a poorer** prognosis, thus the EAG is concerned about the impact of this difference on the results and conclusions drawn about treatment…"*	Suggest text change.	
Section 3.3.1.1, page 59 *"For people receiving placebo there was a worsening of logMAR +0.084; 95% CI: –0.032 to 0.203, which equated to worsening of 4 letters on the ETDRS chart"*	Please amend the text as follows: *"For people receiving placebo there was a worsening of logMAR **+0.085**; 95% CI: –0.032 to 0.203, which equated to worsening of 4 letters on the ETDRS chart"*	Typographical error.	

Section 3.3.1.1, page 59 *"However, when the analysis was based on the mITT population, the difference between treatment groups for all patients was still not statistically significant for the outcome of best recovery of logMAR VA (difference between groups –0.100, 95% CI –0.214 to 0.014; p = 0.0862), corresponding to a 5-letter difference on the ETDRS chart"*	Please amend the text as follows: *"However, when the analysis was based on the mITT population, the difference between treatment groups for all patients was still not statistically significant for the outcome of best recovery of logMAR VA (difference between groups –0.100, 95% CI –0.214 to* ***-0.014****; p = 0.0862), corresponding to a 5-letter difference on the ETDRS chart"*	Typographical error.	
Section 3.3.1.1, page 59 *"Although, in the result for the change in baseline of best VA there was a statistically significant difference between groups in favour of idebenone (logMAR –0.160, 95% CI: –0.289 to –0.031; p = 0.015) that corresponded to an 8-letter difference on the ETDRS chart."*	Please amend the text as follows: *"Although, in the result for the change* ~~***in***~~ ***from*** *baseline of best VA there was a statistically significant difference between groups in favour of idebenone (logMAR –0.160, 95% CI: –0.289 to –0.031; p = 0.015) that corresponded to an 8-letter difference on the ETDRS chart."*	Typographical error.	

Section 3.3.1.3, page 61: *"The EAG notes that the availability of outcome data overtime from the LEROS ITT population was greater than the EAP."*	Please amend the text as follows: *"The EAG notes that the availability of outcome data **over time** from the LEROS ITT population was greater than the EAP."*	Typographical error.	
Section 3.3.1.4, page 63: "*These findings overall demonstrate the rapid and severe vision loss occurs between presentation and nadir; while some degree of VA recovery is possible post-nadir, VA remains severely affected with the majority of patients remaining legally blind."*	Please amend the text as follows: "*These findings overall demonstrate the rapid and severe vision loss **occurring** between presentation and nadir; while some degree of VA recovery is possible post-nadir, VA remains severely affected with the majority of patients remaining legally blind."*	Typographical error.	
Section 3.3.2, page 65: *"In CaRS-I the proportion of patients with spontaneous Clinically Relevant Recovery (sCRR) from VA nadir was also assessed for patients in the Natural History Outcomes population (comprising patients or whom at least 2 VA assessments were…"*	Please amend the text as follows: *"In CaRS-I the proportion of patients with spontaneous Clinically Relevant Recovery (sCRR) from VA nadir was also assessed for patients in the Natural History Outcomes population (comprising patients **for** whom at least 2 VA assessments were…"*	Typographical error.	

Section 3.3.3, Table 16, row 1, column 5, page 67 *"1.16 (-0.18 to 1.80)"*	Please amend the text as follows: *"1.16**±0.55** (-0.18 to 1.80)"*	Typographical error.	Not a factual inaccuracy. No change needed. The EAG has adapted the table provided in the clarification response to not include standard deviations and only include the confidence interval data.
Table 16, row 3, column 4, page 67 *"0.085 (–0.032 to 0.203) [4 letters]"*	Please amend the text as follows: *"0.085 (–0.032 to 0.203) [**-**4 letters]"*	Typographical error.	The EAG thanks the company for highlighting this inaccuracy and has updated the text accordingly.
Section 3.3.5, page 70 *"A total of 42 patients (81.1%) in the idebenone group and 24 patients (82.8%) in the placebo group reported experiencing less fatigue or no change in fatigue levels."*	Please amend the text as follows: *"A total of **43** patients (81.1%) in the idebenone group and 24 patients (82.8%) in the placebo group reported experiencing less fatigue or no change in fatigue levels."*	Typographical error.	

Section 3.3.6, page 70 *"A slightly higher proportion of participants in the idebenone arm reported nasopharyngitis (idebenone: 25.5%; placebo: 16.7%); cough (idebenone: 10.9%; placebo: 0%); dizziness (idebenone: 5.5%; placebo: 0%); and left ventricular hypertension (idebenone: 7.3%; placebo: 0%)."*	Please amend the text as follows: *"A slightly higher proportion of participants in the idebenone arm reported nasopharyngitis (idebenone: 25.5%; placebo: 16.7%); cough (idebenone: 10.9%; placebo: 0%); dizziness (idebenone: 5.5%; placebo: 0%); and left ventricular **hypertrophy** (idebenone: 7.3%; placebo: 0%)."*	Typographical error.	
Section 3.3.6.2, page 74 *"In RHODOS, four (7.3%) idebenone patients compared to 0 (0%) placebo patients experienced left ventricular hypertension"*	Please amend the text as follows: *"In RHODOS, four (7.3%) idebenone patients compared to 0 (0%) placebo patients experienced left ventricular **hypertrophy**"*	Typographical error.	
Section 3.5, page 84 *"No RCT data comparing long-term treatment with idebenone and SoC are available as evidence has been limited to observational data with inherent limitations such the open-label and uncontrolled nature of the data collection in the EAP, the retrospective analysis of patient records…"*	Please amend the text as follows: *"No RCT data comparing long-term treatment with idebenone and SoC are available as evidence has been limited to observational data with inherent limitations such **as** the open-label and uncontrolled nature of the data collection in the EAP, the retrospective analysis of patient records…"*	Typographical error.	

Section 4.2.2.1, page 90-91 *"The EAG additionally considers that that the reduction in health states also makes the best use of the limited available patient data as it avoids the implausible model transitions exhibited in the company's base-case model."*	Please amend the text as follows: *"The EAG additionally considers that* ***~~that~~*** *the reduction in health states also makes the best use of the limited available patient data as it avoids the implausible model transitions exhibited in the company's base-case model."*	Typographical error.	The EAG thanks the company for highlighting this inaccuracy and has updated the text accordingly.
Section 4.2.3, page 91 *"…was based on the UK NHS and PSS (personal and social service), with future costs and benefits discounted using an annual rate of 3.5%, as per the NICE reference case."*	Please amend the text as follows: *"…was based on the UK NHS and PSS (****personal social services****), with future costs and benefits discounted using an annual rate of 3.5%, as per the NICE reference case."*	Typographical error.	
Section 4.2.4.2, page 92: *"…the EAP study was preferred by the company due to the lesser heterogeneity compared to the RHODOS patient populations, with an additional advantaging being the longer study time of the EAP."*	Please amend the text as follows: *"…the EAP study was preferred by the company due to the lesser heterogeneity compared to the* ***LEROS*** *patient populations, with an additional* ***advantage*** *being the longer study time of the EAP."*	Typographical error.	

Section 4.2.4.2.1, page 94 *"The LEROS study is also larger than the EAP (198 vs 87 patients) and therefore using LEROS may have lessened the key issue of missing data, which in combination with the high number of health states, leads to multiple transitions between health states in the model being impossible."*	Please amend the text as follows: *"The LEROS study is also larger than the EAP (**196** vs 87 patients) and therefore using LEROS may have lessened the key issue of missing data, which in combination with the high number of health states, leads to multiple transitions between health states in the model being impossible."*	Typographical error. LEROS ITT population: 196 patients.	
Section 4.2.4.3.1, page 99: *"The EAG consider this approach was preferred to anchoring the idebenone treatment effect to SoC given that the SoC treatment effects from CaRS are highly uncertainty."*	Please amend the text as follows: *"The EAG consider this approach was preferred to anchoring the idebenone treatment effect to SoC given that the SoC treatment effects from CaRS are highly **uncertain**."*	Typographical error.	

Section 4.2.4.3.1, page 99: *"While at 36 months in the scenario, change from baseline logMAR is slightly better that measured in the RHODOS-OFU trial at 36 months (-0.0065 vs 0.039, respectfully)), at the beginning of the model the SoC treatment effect in the LEROS scenario is greatly underestimated compared to the SoC treatment effect in the RHODOS study (6 months) the outcomes of which are less discounted in the model."*	Please amend the text as follows: *"While at 36 months in the scenario, change from baseline logMAR is slightly better* ***than*** *that measured in the RHODOS-OFU trial at 36 months (-0.0065 vs 0.039, respectfully).* ***At*** *the beginning of the model****,*** *the SoC treatment effect in the LEROS scenario is greatly underestimated compared to the SoC treatment effect in the RHODOS study (6 months)****,*** *the outcomes of which are less discounted in the model."*	Typographical error.	
Section 4.2.4.3.1, page 100: *"…however, limited patient observations are used from the studies compared to the potentially appropriate, available and as reported in Section 3.4.2 alternative matching methodologies that could also have been employed."*	Please amend the text as follows: *"…however, limited patient observations are used from the studies compared to the potentially appropriate, available****,*** *and as reported in Section 3.4.2****,*** *alternative matching methodologies that could also have been employed."*	Missing punctuation.	

Section 4.2.6.2, page 105: *"For these utility values to be used it would require making assumptions regarding how the health states match up to the equivalent logMAR score."*	Please amend the text as follows: *"For these utility values to be used**,** it would require making assumptions regarding how the health states match up to the equivalent logMAR score."*	Missing punctuation.	
Section 4.2.6.2, last sentence, page 107: *"Table 26. Estimated utility values by logMAR visual acuity, produced based on Figure 2, Lawrence et al. 2023b."*	Please remove the text as follows: ***~~"Table 26. Estimated utility values by logMAR visual acuity, produced based on Figure 2, Lawrence et al. 2023b."~~***	Formatting error.	
Section 4.2.7.3, page 113: *"In response to a clarification question (question B1), the company also provide the proportion of patients requiring each resource…"*	Please amend the text as follows: *"In response to a clarification question (question B1), the company also **provided** the proportion of patients requiring each resource…"*	Typographical error.	
Section 4.2.7.3.1, page 115: *"One expert stated that they would not expect young people with vision equal to driving vision to be experiencing regular falls, as is estimated by the company's resource use."*	Please amend the text as follows: *"One expert stated that they would not expect young people with vision equal to driving vision to be experiencing regular falls, as **~~is~~** estimated by the company's resource use."*	Typographical error.	

Section 5.2.1, page 120: *"The EAG notes that while the ICER was most sensitive to the utility of patients with a logMAR of less than 0.3, the analysis did not vary treatment effectiveness which the EAG considers the ICER may be most sensitivity to given the results of the EAG scenario conducted."*	Please amend the text as follows: *"The EAG notes that while the ICER was most sensitive to the utility of patients with a logMAR of less than 0.3, the analysis did not vary treatment effectiveness**,** which the EAG considers the ICER may be most **sensitive** to**,** given the results of the EAG scenario conducted."*	Typographical error and missing punctuation.	
Section 5.2.2, Table 34, page 121-122: Missing abbreviations	Please add abbreviations.	Missing abbreviations.	
Section 6.5, page 127: "…*with SoC logMAR worsening 2.28 times as much in the model compared to the end of the RHODOS study (6 months) if considering the mITT population and 3.84 worse with respect to the ITT population"*	Please amend text as follows: "…*with SoC logMAR worsening 2.28 times as much in the model compared to the end of the RHODOS study (6 months) if considering the mITT population and 3.84 **times** worse with respect to the ITT population."*	Typographical error.	

Section 2.2, Page 21 *"LHON causes degeneration of the optic nerve, and people with LHON experience a sudden and rapid loss of central vision, usually within weeks of symptom onset."*	"LHON causes degeneration of the optic nerve, and people with LHON experience a **subacute** and rapid loss of central vision, usually within weeks of symptom onset."	Suggested text change.	Not a factual inaccuracy. No change required.

Issue 11 Confidential mark-up

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 2.3.1, Page 32	AiC mark up to be removed	included patients aged ≥12 years, whose onset of symptoms dated after 1999 and was 'well documeted' (at least the month pf the onset of symptoms was known for each eye), with at least two VA assessments available within 5 years of onset of symptoms and prior to idebenone use, with a genetic diagnosis for LHON for one of the following mtDNA mutations m.11778G>A; m.14484T>C; and m.3460G>A, with no participation in an interventional clinical trial after the onset of symptoms.	The EAG thanks the company for highlighting this inaccuracy and has updated the text accordingly.
Section 3.2.1, Table 11, page 41	AiC mark up for study sites only	In the CSR is specified: the randomisation procedure was centralised [redacted]	

Section 3.2.1, Table 11, page 42	AiC mark up to be removed	of the 85 patients randomised and treated, 7 patients discontinued the study prematurely, 3 patients (5.5%) treated with idebenone, and 4 patients (13.3%) treated with placebo." The most commonly reported reason for premature discontinuation was withdrawal of consent (2 patients treated with idebenone and 1 patient treated with placebo). One patient in each treatment group was withdrawn due to adverse events.	
Section 3.2.3, page 44	AiC mark up to be removed	Patients were seen and followed up after initiating of treatment with idebenone, according to local practice. VA assessments were conducted at regular (generally 3-monthly clinical visits).	
Section 3.2.3, page 45	AiC mark up to be removed	"place at Month 1, Month 3, Month 6, Month 9, Month 12, Month 18 and Month 24".	
Section 3.2.4, page 50	AiC mark up to be removed	who fulfilled the following prospectively defined inclusion criteria: • Age≥12 years; • The onset of symptoms was dated after 1999 and was well documented (at least the month of the onset of symptoms was known for each eye); • At least two VA assessments were available within 5 years of onset of symptoms and prior to idebenone use; • Have a genetic diagnosis for LHON for one of the following mtDNA mutations: m.11778G>A; m.3460G>A or m.14484T>C.	
Section 3.2.5, Table 14 [LEROS:Male, n (%),] page 52	Trial data to be marked up	[redacted]	

Section 3.2.5, Table 14 [LEROS Mutations, n (%)], page 53	Trial data to be marked up	[redacted]	
Section 3.2.5, page 57	Trial information to be marked up	However, it was noted that in the LEROS trial, the proportion of people with the m.11778G>A mutation, was [redacted] compared to the RHODOS trial, the EAP and CaRS.	
Section 3.3.1.4, Figure 4, page 62	Error in the highlighting colour	Please highlight the figure in turquoise.	The EAG thanks the company for highlighting this inaccuracy and has updated the highlighting colour.
Section 3.3.1.4, Figure 5, page 63	Error in the highlighting colour	Please highlight the figure in turquoise.	The EAG thanks the company for highlighting this inaccuracy and has updated the highlighting colour.
Section 3.4.2, Table 18 [Matched idebenone (LEROS)	Trial data to be marked up	[redacted]	The EAG thanks the company for highlighting this inaccuracy and has updated the text accordingly.

Genotype], page 77			

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