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:

1. **Draft Guidance Document 2 (DG2)** as issued to consultees and commentators

2. **Comments on the Draft Guidance 2 from** Chiesi
   a. Response to draft guidance 2
   b. Draft guidance 2 appendix

3. **Consultee and commentator comments on the Draft Guidance 2** from:
   a. LHON Society
   b. Patient expert Lily Mumford

4. **Expert personal perspectives** from:
   a. Mary Clifford, patient expert nominated by LHON Society

5. **Clarification on the Draft Guidance 2 response from Chiesi**

6. **External Assessment Group (EAG) critique of company response to the Draft Guidance 2**

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

Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using idebenone in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: February 2025

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using idebenone in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 26 March 2025
- Third evaluation committee meeting: To be confirmed
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Idebenone is not recommended, within its marketing authorisation, for treating visual impairment in Leber's hereditary optic neuropathy (LHON) in people 12 years and over.

1.2 This recommendation is not intended to affect treatment with idebenone that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare practitioner consider it appropriate to stop. For young people, this decision should be made jointly by them, their healthcare practitioner, and their parents or carers.

Why the committee made these recommendations

Standard care for LHON includes nutritional supplements, genetic counselling and lifestyle management advice. There are no licensed medicines for the underlying causes of LHON, so there is an unmet need for new treatments.

Evidence from a clinical trial directly comparing idebenone with standard care suggests that idebenone may be no better at improving vision. But this is uncertain because the trial only included a small number of people and was short. Longer-term trials show that idebenone improves vision but, in these trials, it was not compared with standard care. An indirect treatment comparison also suggests that idebenone may be no better than standard care at improving vision in the long term. Overall, it is uncertain how effective idebenone is compared with standard care, and further research is needed to estimate its potential benefits.

The clinical-effectiveness uncertainties are also present in the economic model, leading to uncertainty in cost-effectiveness estimates. Idebenone is not recommended because of these uncertainties and because the most likely cost-effectiveness estimate is substantially above the range NICE normally consider to be an acceptable use of the NHS resources.

2 Information about Idebenone

Marketing authorisation indication

2.1 Idebenone (Raxone, Chiesi) is indicated for the 'treatment of visual impairment in adolescent and adult patients with Leber's hereditary optic neuropathy (LHON)'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for idebenone.

Price

2.3 The list price for a 180 tablets pack of 150 mg idebenone is £6,364 (excluding VAT; BNF online, accessed April 2024).

2.4 The company has a commercial arrangement, which would have applied if idebenone had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Chiesi, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

Clinical management

The condition

3.1 Leber's hereditary optic neuropathy (LHON) is caused by mutations in the genes encoding mitochondrial DNA (mtDNA). Mutations in mtDNA disrupt the synthesis of adenosine triphosphate (ATP) and produce free radicals. This damages retinal ganglion cells and destroys the optic nerve. LHON is normally inherited, if a mother carries the mutation, it may be transmitted to children. The 3 most common mutations are 11778G>A, 14484T>C and 3460G>A. These mutations are found in around 95% of the LHON population. LHON typically leads to progressive vision loss, particularly in

young adults, and mainly affects boys and men. The patient experts explained that the experience of living with LHON varies from person to person. They explained that, for them, LHON:

- came on rapidly
- is painless
- is subacute
- has caused severe loss of visual acuity (VA) and colour vision, and loss of central but not peripheral vision.

They explained that, even though peripheral vision is usually preserved initially, it may also deteriorate over time. This can lead to being registered as blind. Blurring and clouding of vision are usually the first symptoms of LHON and start in 1 eye, with the second eye following a similar progression within 4 to 6 months. The clinical experts explained that LHON is usually irreversible, but that spontaneous improvement may occur in a few people with certain LHON mutations such as 14484T>C and 3460G>A. The clinical experts noted the lack of understanding of the cause and natural history of LHON. Its course is split into subacute, dynamic and chronic phases. But this naming convention has limited significance because each phase may present differently for different people. There is what is described as a nadir, or lowest point, of VA, after which no further deterioration in central vision is expected. This may be different for each person with LHON. The committee noted the frequent rapidity of progression of LHON and the uncertainty around the mechanism of disease activity.

Unmet need

3.2 There are no licensed treatments for LHON available in the NHS in England. The clinical and patient experts explained that the rapid vision loss and deteriorating nature of the condition have a considerable effect on people's:

- independence

- education
- ability to work and occupational choices
- social life
- ability to carry out day-to-day tasks.

The patient experts explained that the condition significantly affects the lives of people with LHON because it leads to a sudden and severe loss of central vision in 1 eye then, shortly afterwards, in the other eye. In most people, chronic visual impairment remains. The sudden change in sight can make daily activities such as reading, driving, travelling on public transport and recognising faces very difficult. The patient and clinical experts explained that many people must adapt to their reduced vision. This can include relying on assistive technologies, such as screen readers, magnifiers or speech to text software to access digital information. Also, people with LHON can feel emotional and psychological effects, including grief, frustration, anxiety and depression, and coping with vision loss also affects their families and carers. The effects can lead to an inability to work and socialise, a negative effect on education, missed career opportunities and difficulties in having relationships. The clinical experts explained that carers are often the family members of people with LHON, specifically mothers who may feel guilt for passing on the condition. The committee understood that there are no treatment options and people with LHON often have difficulty doing daily tasks. It also understood that the condition can have an impact on education, independence, travelling on public transport and career opportunities, cause financial burdens for people and their families, and result in difficulties in having relationships. The committee concluded that LHON is a rare, serious and debilitating condition that severely affects the lives of people with it, and their families and carers.

Existing treatment

3.3 The patient and clinical experts explained that no treatment addresses the underlying cause of LHON. They explained that the current treatment option for people with LHON is limited to best supportive care (standard care from now). This includes neuro-ophthalmology outpatient appointments, referral to low-vision services, lifestyle advice and genetic counselling. They explained that genetic counselling can help people with LHON and their carers understand the condition, risk factors and its inheritance. Supportive therapies such as low-vision aids and infrared light therapy may be used to help people to adjust to changes in vision and maintain independence. Lifestyle modifications are often recommended for people with LHON. These can include avoiding certain things that could potentially worsen their condition, such as tobacco, alcohol and exposure to drugs and toxins with mitochondrial toxicity. Ubiquinone (coenzyme Q10) and other substances can be used to improve mitochondrial function, reduce oxidative stress and provide alternative ATP energy sources. The clinical experts clarified that ubiquinone may be effective in other mitochondrial conditions. But they noted that the evidence suggests it is not very effective in treating LHON because it does not pass the blood-brain barrier to get to the optic nerve. The committee noted that managing LHON is complex and individualised, and that there is no effective treatment for LHON. It concluded that standard care is the appropriate comparator and would be given in addition to idebenone.

Clinical-effectiveness evidence

Data sources for idebenone

3.4 For the clinical effectiveness and safety of idebenone in people with LHON, evidence from 5 studies was considered. These were:

- RHODOS: a double-blind randomised placebo-controlled trial assessing the efficacy and safety of idebenone in 85 people over 24 weeks of treatment. It included people aged 14 to 64 years with impaired VA in at least 1 eye because of LHON with an onset of visual

loss of 5 years or less, and a confirmed diagnosis (m.11778G>A, m.14484T>C or m.3460G>A LHON mtDNA mutations identified).

- RHODOS observational follow up (OFU): a single-visit observational follow-up study of 58 people with LHON assessing the long-term efficacy of idebenone. It included people in the RHODOS trial in either the idebenone or placebo arms, but who were not expected to have idebenone after RHODOS finished. Median follow up was 30 months (range: 20.9 to 42.5 months).
- LEROS: an open-label intervention study assessing the efficacy and safety of long-term treatment with idebenone in 199 people 12 years and over with LHON. It lasted 24 months, with visits taking place at months 1, 3, 6, 9, 12, 18 and 24.
- Expanded access program (EAP): a real-world-evidence open-label multicentre retrospective analysis of long-term treatment with idebenone in 111 people with LHON with an onset less than 5 years from baseline. It included people 12 years and over with vision loss of less than 12 months before starting idebenone.
- PAROS: a phase 4 study, post-authorisation study with the primary objective to evaluate the long-term safety profile of idebenone in the treatment of people with LHON.

The committee noted that the main evidence came from RHODOS. LEROS and EAP provided data on the long-term effectiveness of idebenone for LHON. The committee noted that RHODOS was a high-quality randomised controlled trial (RCT), but had a small sample size and provided limited evidence on the long-term effects of idebenone. RHODOS-OFU provided data that was based on a single visit 30 months after RHODOS finished. The people included did not have idebenone between the end of RHODOS and their follow-up visit. The EAP provide long-term data on people with LHON who had idebenone on an individual basis for 36 months. The committee noted that, when the RHODOS study was started, there was a lack of detailed natural history studies on LHON. Also, the optimum length of time needed to

detect the impact of treatment was not known. So, further non-randomised studies such as the EAP, LEROS and PAROS were included in the idebenone development program.

Comparator data (CaRS natural history studies)

3.5 For the first committee meeting, the company used data from the case record survey (CaRS) natural history studies to inform the comparative effectiveness of the standard-care comparator. This was because of the lack of long-term RCT data in the EAP, RHODOS-OFU and LEROS. The CaRS studies were retrospective non-interventional studies of existing medical records of people with a genetically confirmed diagnosis of LHON. The EAG explained that the CaRS studies had a large proportion of missing data, and a high degree of variability in the availability of data from people with LHON at different time points. The committee noted that the lack of long-term comparator data meant that the company used an indirect treatment comparison (ITC) to compare idebenone with standard care. The committee noted that the CaRS studies were international studies with CaRS-1 reporting natural history data for 383 people with LHON and CaRS-2 reporting natural history data for 219 people with LHON. The committee noted that the CaRS studies did not provide direct evidence on long-term treatment with idebenone compared with standard care. It also noted that there was a lot of missing data and a high degree of variability in the availability of data from different people at different time points. The committee concluded that using data from the CaRS studies was acceptable to inform comparative effectiveness in the context of this evaluation. But it thought that further characterisation of natural history using the data could be attempted, rather than only using a limited number of data points.

Integrated data set

3.6 In response to consultation, the company did an integrated analysis to address the committee's concerns about the lack of comparative data between idebenone and standard care. The integrated data was done using, RHODOS-OFU, EAP, CaRS-1, CaRS-2, LEROS and PAROS. It

included data from 1,252 people, of whom 847 were included in the intention-to-treat (ITT) analyses. This included 409 people having idebenone and 438 people having standard care. The committee noted that the company did not include RHODOS 6-month RCT data in the integrated analysis.

Outcomes

3.7 RHODOS measured outcomes such as VA, clinically relevant recovery, contrast sensitivity, visual field assessment and adverse effects. It provided analyses for many outcomes at the level of an individual eye (for example, change in the logarithm of the minimal angle of resolution [LogMAR] VA of individual eyes) and at the level of the patient (for example, change in the LogMAR VA of a patient's best eye). It based its economic model on VA based on the LogMAR VA transitions seen in the clinical evidence. The company noted the difficulty in collecting outcome data on VA and relating it to quality of life for LHON. This was because both eyes may be affected at different time points, so each person's VA at baseline was not always clear. The EAG thought that the change in a person's best eye would most closely be linked to quality of life. The patient experts explained that, during their visual field assessment, they noted that their peripheral vision improved over time to compensate for losses in central vision. They thought this might explain minor improvements in VA without idebenone. The committee was aware that common outcomes used to evaluate best VA and colour sensitivity were presented as secondary outcomes. The committee agreed that the best VA was broadly acceptable as an outcome to inform the assessment of efficacy of idebenone. But it noted potential limitations of the sensitivity of the outcome if describing smaller treatment effects.

Results

3.8 In RHODOS, the primary outcome was best recovery of VA for people with improving VA in either eye or least worsening of VA for people whose VA was not improving in either eye, between baseline and week 24. This

was identified using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart and expressed using LogMAR values. The primary outcome improved both for people having idebenone and people having placebo. With idebenone, there was a mean LogMAR improvement of -0.135 (95% confidence intervals [CI] -0.216 to -0.054). This equated to an improvement of 6 letters on the ETDRS chart. With placebo, there was a LogMAR improvement of -0.071 (95% CI -0.176 to 0.034). This equated 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; p=0.291). This equated to a 3-letter change. In the RHODOS ITT population, for the change in best VA in the best eye at week 24 compared with the best VA in the best eye at baseline, the difference between idebenone and standard care did not reach statistical significance. In people having idebenone, the LogMAR slightly improved (change -0.035, 95% CI -0.126 to 0.055), which equated to an improvement of 1 letter on the ETDRS chart. For people having placebo there was a worsening of the LogMAR (change +0.085, 95% CI -0.032 to 0.203), which equated to a 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; p=0.078) and equated to a 6-letter change. In the RHODOS trial, a higher proportion of people in the idebenone group (ITT 30.2%; n=16) than in the placebo group (ITT 10.3%, n=3) showed clinically relevant recovery (CRR) from baseline. The difference between the groups was not statistically significant (p=0.056).

The committee noted that the statistically significant changes in the best VA and VA of the best eye from baseline did not reach statistical significance. It acknowledged that even a small improvement in vision would be important, particularly for people with severe sight impairment. The company explained that RHODOS was short and was completed before a wide understanding of the natural history of LHON. So, it may not have shown the true benefit of idebenone. It presented further non-randomised evidence from longer-term trials from EAP and LEROS. In

EAP, there was a slight improvement in best VA. The LogMAR decreased 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 LEROS, there was also a slight improvement in best VA from baseline to 24 months (ITT population). There was a mean change in the LogMAR of -0.09 in people with LHON onset in the second eye of 1 year or less and a change in the LogMAR of -0.19 in people with LHON onset in the second eye of more than 1 year. The committee concluded that the evidence suggested that idebenone may have some benefit in terms of improving vision, and preventing vision deterioration and progression of LHON. But it thought that the results were uncertain because of the non-randomised nature of the available long-term evidence.

Generalisability

3.9 The committee noted small differences in baseline characteristics such as age and sex between individual studies, and between RHODOS (used in the updated company model from 0 to 6 months) and the integrated analysis (used in the company model from 6 months). The EAG's clinical experts thought that age at baseline and sex are not prognostic factors for LHON, so this was unlikely to have affected the results. The clinical experts explained that RHODOS was a small study that had a different profile of mutations compared to larger studies. They explained that some mutations were underrepresented and some were overrepresented in RHODOS. The committee was aware that the proportion of people with the m.11778G>A mutation (associated with a lower rate of spontaneous improvement) was higher in RHODOS compared with the integrated analysis. It particularly noted that m.14484T>C (associated with a higher rate of spontaneous improvement) was overrepresented in RHODOS compared with the integrated analysis. The clinical experts explained that overrepresentation of this mutation could have led to standard care performing better in RHODOS than would be expected in the NHS. The EAG explained that the results of a subgroup analysis of idebenone compared with standard care, which excluded m.14484T>C, did not reach statistical significance. The clinical experts explained that the proportion of

the most common mutation (m.11778G>A) in clinical practice is more similar to that in the RHODOS than in the integrated analysis. The committee also noted that the proportion of people with a LogMAR above 1 was 85% in RHODOS compared with 55% in the integrated analysis. The clinical experts explained that, in their experience, over 90% of people present to their services with a LogMAR above 1 because early diagnosis is very uncommon. The committee noted considerable uncertainty with the generalisability of the evidence. It concluded that RHODOS was potentially more generalisable to NHS clinical practice. This was based on the proportion of people with the m.11778G>A mutation and the proportion of people with a LogMAR above 1 more closely resembling the proportions that would be expected in the NHS.

Establishing relative treatment effect

3.10 A direct comparison between idebenone and standard care was only available for 6 months. After this, no direct evidence was available comparing idebenone with standard care. At the first committee meeting the company derived relative treatment effects of idebenone compared with standard care from an ITC using 2 unmatched populations. These were the EAP population for idebenone and the CaRS natural history studies. The EAG noted that the imbalance in prognostic factors between the EAP and the CaRS studies, for example, the study differences in the prevalence of 3 mutations. The EAG explained that this could have biased the result of the ITC. So, it thought that matching the idebenone and standard-care cohorts would be less biased. At the clarification stage, the company provided a propensity score-matching analysis (PSM) of changes in best VA between LEROS and CaRS-1 and CaRS-2 at month 24. The EAG thought that, after matching, the baseline characteristics were reasonably balanced between LEROS and CaRS-1 and CaRS-2. But it noted that the age of first symptom onset was younger in the standard-care cohort than the idebenone cohort. Also, the prevalence of T14484C genotypes was higher in the idebenone cohort than in the standard-care cohort. The EAG commented that only a limited amount of the CaRS follow-up data was included in the PSM analyses.

This was because the company chose to only analyse a single-visit pair (from baseline to 24 months), rather than all available data for standard care. The EAG commented that the median time between visits was 11.7 months in the CaRS studies. So, restricting the analysis to visit pairs 24 months apart likely did not use all the available data. It preferred matching people between LEROS and the CaRS studies at baseline and using all available follow-up data in the analysis. The committee noted that the results of the ITC suggested that idebenone appeared to improve change in best VA at 24 months by -0.02 on the LogMAR scale. This meant it was slightly more effective than standard care in improving VA. But this was not statistically significant, which meant that it was likely that there was no evidence of a difference in treatment effect between idebenone and standard care. The committee understood that PSM did not provide reliable evidence of the long-term treatment benefit of idebenone compared with standard care. But it thought that there were substantial uncertainties in the methods of the ITC because of the limitations of the evidence and limited time in which it had to be completed. The committee thought that there was insufficient sensitivity analysis and exploration of uncertainty of the population adjustment used in the ITC. There were also considerable limitations in the methodology of only using patient-level data for beyond 24 months in the CaRS dataset. So, it requested analyses based on a more comprehensive view of the entirety of the available CaRS evidence.

During consultation, the company did an integrated analysis (see section 3.6) to estimate treatment effect. This was used in the model after 6 months. As part of this, the company presented a propensity score weighted analysis (PSWA) to address the imbalance between idebenone and standard care requested by committee. The company's PSWA was a weighted stabilised inverse probability of treatment weights computed by a propensity score model. Sex, age at onset, time from onset at baseline, baseline best-corrected VA, unilateral or bilateral involvement at baseline and type of mutation (that is, G11778A, G3460A, T14484C) variables

were included in the analysis. The committee noted that some potential prognostic factors, such as timing of nadir, were not included in the analysis. The EAG thought that the updated propensity score weighting was potentially less biased than original approach.

The EAG explained that the RHODOS was used to calculate transition probabilities for the first 6 months in the model (see section 3.11) but was not accounted for in the company's integrated analysis. The committee questioned the validity of excluding RHODOS from the integrated analysis (see section 3.6). The company clarified that it had excluded RHODOS because it was an RCT. Also, its integration with observational and retrospective studies would have introduced bias because of differences in study design. The EAG explained that the company's approach may not have been coherent. This was because it did not make the populations in the integrated analysis similar to those in RHODOS, despite using both data sources in the model. The committee noted that the company did not provide the results of 6 months of analysis including and excluding RHODOS, which was requested by the EAG at clarification. The committee concluded that it would have liked to have seen the impact of including the RHODOS data in the integrated analysis or use of PSWA to match the integrated analysis with the RHODOS data.

Economic model

Company's model structure

3.11 The company presented an economic model comparing idebenone with standard care. The model was based on a Markov state transition model that included 8 health states and an absorbing death state. Health states were based on VA expressed using the LogMAR (LogMAR less than 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.) counting figures, hand movement and light perception. The company explained that its model structure was in line with model structures used in NICE's highly specialised technologies guidance on voretigene neparvovec for treating inherited retinal dystrophies caused by

RPE65 gene mutations (from now, HST11) and NICE's technology appraisals guidance on ranibizumab for treating diabetic macular oedema, ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion and ranibizumab for treating choroidal neovascularisation associated with pathological myopia. The patient and clinical experts agreed that the company's 8 health state model accurately captures the natural progression of LHON. At the second meeting, the committee noted that the EAG agreed with the 8 health-state model. The committee concluded that the 8 health-state model was appropriate for decision making.

Baseline distribution and model outputs

3.12 In response to consultation, the company derived transition probabilities for idebenone and standard care using:

- RHODOS: baseline to month 6
- integrated analysis (month 6 to month 12): with propensity score weights based on stabilised inverse probability of treatment weights
- integrated analysis (month 12 to month 36): weighted and estimated using a logistic regression model with missing at random and missing not at random assumptions
- no change in LogMAR: month 36 onwards.

The company explained that the baseline population distribution used in the model was based on the integrated analysis ITT baseline distribution. This included RHODOS and had a large sample size. The EAG preferred to use RHODOS to inform baseline characteristics and distribution in its model. This was because RHODOS was used to model transitions from baseline to month 6. The committee noted that the source of baseline distribution had a large impact on the cost-effectiveness results. This was mainly because more people started in better health states (lower LogMAR) when the integrated analysis distribution was used (see section 3.9). This led to greater quality-adjusted life year (QALY) gains once the transition probabilities were

applied.

The company thought that the change in LogMAR from baseline predicted by its model using the baseline distribution from the integrated analysis aligned well with:

- the results of the RHODOS trial at 6 months
- the outputs of the integrated analysis across all timepoints.

The exact values for change in LogMAR from baseline estimated in the model is considered confidential by the company so cannot be reported here. The EAG thought that it was important to align the model outcomes with the RHODOS outcomes. It thought that the company's approach overestimated the deterioration in LogMAR for standard care compared with RHODOS at 6 months. It explained that using RHODOS baseline distribution led to outputs that more accurately captured the RHODOS trial effect outcomes. The clinical experts noted that the EAG's approach more accurately reflected the RHODOS standard-care outcomes at 6 months. But they thought that, in the longer term, the EAG's approach suggested an improvement in outcomes over time. They explained that this would not be expected in clinical practice. The committee acknowledged the clinical experts' concerns, but recalled that it had heard there can be some improvements in vision over time with standard care (see section 3.7). It also thought that the improvements from baseline were relatively small. The committee thought that the most important thing to consider was the difference in change in LogMAR from baseline between the treatment arms. The company's model predicted a much bigger improvement than the EAG's approach. The committee noted the small non-statistically significant difference in efficacy in the RHODOS trial (see section 3.8). So, it thought that the outputs of the EAG's model had more face validity. The committee also recalled that the RHODOS population may have been more reflective of the NHS than the integrated analysis population (see section 3.9). So, the committee concluded that it was

more appropriate to use the baseline distribution from RHODOS. But the committee acknowledged that the EAG's approach was imperfect. This was mainly because there was no alternative to applying the integrated analysis at 6 months. The committee thought that the issues with the EAG's approach could have potentially been avoided if RHODOS had been included in the integrated rather applying treatment effect separately.

Time on treatment

3.13 At the first meeting, the committee noted that both the company and the EAG assumed that people would stay on idebenone for up to 3 years. The company used pooled time on treatment data seen in RHODOS and the EAP to model time on treatment with idebenone. The committee noted that clinical opinion received by the EAG suggested that people may continue to have idebenone for more than 3 years if LHON responds to idebenone or has only recently stabilised. The committee noted that the company thought extrapolating beyond 3 years was highly uncertain and inappropriate. This was because of a lack of data because of the small number of people who had treatment for more than 3 years. The patient experts mentioned that they expect idebenone to be used until LHON stabilisation. The clinical experts explained that, in clinical practice, they would use idebenone for up to 2 years if LHON is responding or until LHON stabilisation. They explained that, based on the evidence from the natural history studies and RHODOS, cell death does not continue in LHON for the rest of a person's life. People with LHON do not have repeated episodes of cell death, either with or without treatment over time. The committee was aware that treatment duration ranged from 2.4 to 70.4 months in the EAP study. The committee noted that, in clinical practice, people may have idebenone for longer than 3 years and that this would likely be driven by LHON stabilisation. At the first meeting, the committee concluded that the time on treatment for idebenone was uncertain. It added that it would like to have seen further sensitivity analyses using alternative assumptions from expected use in clinical practice (for example, using assumptions about stability from the available

clinical data).

In response to consultation, the company noted variability in treatment duration across the LHON studies. It modelled time on treatment for idebenone using data from the integrated analysis set. This was based on the time from the first dose to the 'indication' for when the treatment should be stopped based on clinical expert opinion in its base case. This was defined as:

- the first CRR is seen in 24 months, but no additional CRR is seen in the 6 months after the first CRR
- the second CRR is seen in the 6 months after the first CRR, but no additional CRR seen in the 6 months after the second CRR.

CRR was defined as an improvement of at least 2 lines in best-corrected VA or a change from off-chart to on-chart results by at least 5 letters. The company proposed that this could be translated into the following stopping rule in clinical practice:

- People will stay on treatment for a minimum of 24 months if there are no issues with tolerability.
- People who have not had a CRR within 24 months will stop treatment.
- People who have a CRR will stay on treatment until the improvement has plateaued for 2 successive periods (that is, there is no further improvement in VA at the following visit) up to a maximum treatment duration of 36 months.

The EAG thought that it was more appropriate to model time on treatment using the actual treatment discontinuation data from the integrated analysis, which was longer than the company's time on treatment. Importantly, a significant proportion of people had treatment beyond 36 months. The exact figures are considered confidential by the company so cannot be reported here. The committee sought advice from the patient and clinical experts on the acceptability of the

company's proposed stopping rule and appropriateness for use in clinical practice. The clinical and patient experts broadly agreed that the company's proposal of how idebenone would be stopped reflected clinical practice. The clinical experts clarified that, based on International Consensus Statement on the Clinical and Therapeutic Management of LHON 2017, there was a strong consensus that treatment with idebenone should continue for up to at least 24 months. They explained that, if the disease does not respond by 24 months, treatment should be stopped. But disease response can vary from person to person, and they would want to carry on treatment as long as there is a response. Generally, there is a plateau in improvement at 36 months. But there will be some people who may still see improvement after 36 months. For these people, the clinical experts would want the flexibility to carry on treatment. The patient experts explained that, although they experienced anxiety at the thought of stopping treatment, most benefit is derived from having idebenone at the early onset of the disease. They said that they thought it would be appropriate to stop treatment when disease response reaches the stabilisation phase. But they also expressed their concerns about feeling anxious if their disease worsens. The committee noted that both clinical and patient experts agreed that, in clinical practice, there would be some people who would want to have the treatment beyond 36 months, and for whom this would be appropriate. So, the committee was concerned that idebenone may not be used in line with the company's proposed stopping rule. It also noted that the efficacy in the model was based on treatment duration in the integrated analysis set. It added that the company had not proposed any adjustments to reflect the treatment duration associated with the stopping rule. So, the committee thought that the EAG's approach was more appropriate. The committee was aware that this had a large impact on the cost-effectiveness results. It concluded that it would like to see more evidence from the clinical and patient experts about the feasibility of the

company's proposed stopping rule, and efficacy results that took account of it.

Health-related quality of life

3.14 In RHODOS, health-related quality-of-life data was collected using the Visual Function Index (VF-14), Clinicians Global Impression of Change and energy levels. The committee was aware that the NICE reference case recommends using EQ-5D-3L directly measured from people with a condition. When EQ-5D-3L is not available from clinical trial data, EQ-5D data can be sourced from published literature or estimated by mapping from other measures of health-related quality of life collected in clinical trials, using published mapping algorithms. The company explained that no published mapping algorithm was available to map from VF-14, collected in RHODOS, to the EQ-5D. So, it used health-state utility values from Brown et al. (1999) derived from using time trade-off valuation from 325 people with vision loss caused by a range of vitreoretinal conditions. Most people had age-related macular degeneration (33%) or diabetic retinopathy (33%). This was in line with HST11 and NICE's technology appraisals guidance on ranibizumab for treating diabetic macular oedema, ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion and ranibizumab for treating choroidal neovascularisation associated with pathological myopia. The committee noted that the company also provided scenarios using alternative utility values identified by Lawrence et al. (2023), Czoski-Murray et al. (2009) and Rentz et al. (2014). The EAG explained that the utility values from Brown et al. were not based on EQ-5D-3L, and had a higher average age than people with LHON, US-based population. So, the EAG preferred to use utility values from Lawrence et al. in its base case. In this study, EQ-5D data was collected from people in the UK with LHON with an average age of 46.5 years. The committee noted that the source of utility values had a minimal effect on the cost-effectiveness results in the EAG's base case. But it noted that this could have been, in part, because of the alternative model structure used by the EAG. At the first meeting, the committee concluded that Lawrence et al. was a more appropriate source

to derive utility values from. It added that it would like to see further scenarios explored using varying utility values, in particular for reflecting a counting-fingers health state.

In response to consultation, the company updated its model using utility values from Lawrence et al. based on Health Utility Index-3. The company thought that HUI-3 utility values were more appropriate and in line with previous NICE technology appraisal guidance for measuring health-related quality as compared with EQ-5D, which does not have a specific domain for visual impairment. It explained that the HUI-3 used in the Lawerence et al. study measures quality of life specifically related to vision loss in LHON and collected from the UK and Republic of Ireland population with an average age of 46.5 years. The committee noted that the EAG used utility values from Lawrence et al. based on EQ-5D in its base case. It was aware that it had done this because EQ-5D is used as a standard for deriving utility for QALYs, ensuring consistency across evaluations. The committee noted that the company preferred to use HUI-3 values instead of EQ-5D. This was because HUI-3 contains a vision component while EQ-5D is known to have poor convergent validity in visual disorders. Although the EQ-5D measurement method is preferred to measure health-related quality of life in adults. It recalled that, in some circumstances the EQ-5D may not be the most appropriate measure. To make a case that the EQ-5D is inappropriate, qualitative empirical evidence should be provided on the lack of content validity for the EQ-5D, showing that key dimensions of health are missing as described in NICE's manual on health technology evaluation. No empirical evidence was presented by the company. But the committee recognised the difficulties in the ability to collect or generate clinical evidence in a rare condition and determined that it would consider HUI-3 utility values in its decision making. The committee concluded that, in this case, it would consider utility values generated using the HUI-3.

Carer disutility

3.15 The committee noted that the company applied a utility decrement of 0.04 in line with HST11 for all people with a LogMAR of more than 1.0 to represent the disutility associated with LHON caregivers health-related quality of life. The clinical and patient experts explained that most people with LHON need constant support from family members and carers. A patient organisation submission highlighted that a child's diagnosis can have a significant effect on some parents' mental and physical wellbeing. The committee noted there may be effects on carers' quality of life, particularly for younger people with LHON. But it highlighted that the reference case refers to health-related quality of life because of LHON. So, it may be difficult to interpret this in the context of adults with LHON that live independently without fulltime carers. The committee noted that it had not been presented with evidence for carer quality of life associated with LHON. It also noted that the committee for HST11 thought that it was appropriate to apply carer disutilities for parents of children with a condition that causes blindness. But this was not applied to adults. So, it concluded that the EAG's approach of excluding disutility values for carers of adults in all health states could be appropriate, but it could consider scenarios including a carer disutility for adults with LHON if more quantitative evidence for carers of adults with LHON or other conditions that cause blindness was provided.

In response to consultation, the company maintained its position that although, in HST11, there was a carer disutility applied for parents of children with a condition that causes blindness but not carers of adults with LHON . It thought that it was appropriate to include caregiver disutility in the base case. This was to accurately reflect the impact that LHON has on caregiver quality for adults with the condition having a substantially challenging change in their daily living. The patient experts explained that LHON typically begins in early adulthood and affects people between their late teens and early adulthood. They explained that support for LHON-related vision loss is good in childhood, but tends to decline in adulthood. This can leave people to rely on their carers for many daily activities,

including travelling to schools, universities and medical appointments, and using reading or technical equipment that is critical for people to be as independent as possible. The committee noted comments from stakeholders that the effect of LHON on the quality of life of families and carers should be taken into account. The committee acknowledged that adults with LHON may need some assistance in using public services for travelling, and that this could potentially have an effect on the quality of life of families and carers. It noted that it had not seen any evidence to support carer disutility for adults with LHON. It concluded that it would like to see the amount of assistance and impact on carer's quality of life quantified, including the number of carers per patient and the impact of treatment on carer quality of life.

Health-state resource use

3.16 The committee noted that the company included resource costs for each health state, assuming costs associated with blindness using Mead et al. (2003). It included costs of hospitalisations (assumed to be because of injurious falls), outpatient visits (obtaining low-vision aids and rehabilitation), blind registration, supportive living, residential care (aged 65 years and over) and depression. 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 explained that Meads et al. was not specifically based on people with LHON. It also had an older population who were classed as blind, so the reported resource use did not apply to the LHON population. So, it used estimates of each resource across the included model health states (on-chart), classified by the LogMAR value, from a survey of 3 international ophthalmologists. These estimates were validated by the 5 UK clinical experts. The EAG noted uncertainty in the estimates provided by the experts. For example, a wide range between the highest and lowest estimates was provided for many resource categories. The EAG noted that 1 expert said that they would not expect young people with vision equal to driving vision to fall regularly, as estimated by the company's resource use. The EAG explained that, in clinical practice, people who would incur health resource

costs would be clinically visually impaired with a LogMAR of 1.0 to 1.3. So, the EAG only applied resource costs to people with a LogMAR of more than 1, except depression costs, which were assumed to apply to all health states. The clinical experts explained that they would expect costs for outpatient visits for low-vision aids and rehabilitation for people with a LogMAR of less than 1. The committee noted that although there were significant differences in the approaches used by the company and the EAG about the use of health-state resource utilisation, this had a minor impact on the cost-effectiveness results. It concluded that it was appropriate to apply the resource costs of outpatient visits (including obtaining low-vision aids and rehabilitation) for health stages with a LogMAR of less than 1.

In response to consultation, the company clarified it had removed the blind registration fee based on clinical opinion. It explained that it applied resource use as a mid-point proportion informed by clinical opinion and Mead et al., with outpatient care cost as a one-off cost and with supportive living applied across the life horizon. The committee noted that the EAG's applied resource use was based on Mead et al. It included one-off supportive living costs and standard care needing half the outpatient visits compared with idebenone. The committee concluded that using different approaches to calculate health-state resources used had a minor effect on cost-effectiveness results.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.17 The committee noted that the company's updated deterministic base case gave an incremental cost-effectiveness ratio (ICER) below £30,000 per QALY gained for idebenone compared with standard care. The EAG made several changes to the company's base case. These changes increased the cost-effectiveness estimates to a level that was above what NICE normally considers an acceptable use of NHS resources. The committee noted that the EAG's deterministic base case showed that

ICERs for idebenone compared with standard care were over £373,292 per QALY gained. The committee was also presented with a range of scenarios investigating the impact of different assumptions on the company's base case. The committee noted that there was still a high level of uncertainty concerning:

- exclusion of RHODOS from the company's PSWA (see section 3.9)
- using the baseline distribution from the integrated analysis instead of RHODOS (see section 3.11)
- when people would stop idebenone in clinical practice (see section 3.15)
- lack of quantifiable evidence on carer disutility (see section 3.15).

Acceptable ICER

3.18 NICE's manual on health technology evaluation notes that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee was aware that it may accept a higher degree of uncertainty when evidence generation is particularly difficult because the condition is rare. It noted that several of the key uncertainties were affected by the rarity of LHON. These included limited evidence on the long-term effects of idebenone and the assumption used to model the standard-care treatment effect. So, the committee concluded that an acceptable ICER would be towards the upper end of the range NICE considers a cost-effective use of NHS resources (around £30,000 per QALY gained).

Committee's preferred assumptions

3.19 The committee agreed that its preferred assumptions to compare idebenone with standard care included:

- baseline characteristics and distribution of patients based on RHODOS and 8 -health-state model (see section 3.11)
- time to treatment discontinuation based on time on treatment from the integrated analysis (see section 3.15)
- HUI-3 utility values from Lawrence et al. (2023; see section 3.16)
- no carer disutility for LHON adults (see section 3.17).

When taking into account all the committee's preferred assumptions, the ICER for idebenone compared with standard care was 280,416 per QALY gained.

Other factors

3.20 Because of the rarity of LHON, the committee recognised difficulties in the ability to collect or generate clinical evidence on idebenone's comparative effectiveness and the natural history of LHON. It agreed that this contributed to significant uncertainty in decision making. The committee also noted that there may be other factors not included in the analysis. These included the potential of idebenone to reduce anxiety and depression, and the effect of LHON on education, travelling and career opportunities from vision loss. The committee thought that, because of these factors, it would apply greater flexibility in accepting a higher degree of uncertainty, as described in section 6.2.34 of NICE's manual on health technology evaluations. The committee also accepted utility values based on HUI-3 from Lawrence et al. (2023).

Equalities

3.21 The committee was aware that the population for which idebenone is indicated included young people and adults. The committee noted that LHON is a genetic condition. It was aware that LHON is a devastating condition that can begin at a very young age and that people with the condition, and their families and carers, are affected in all aspects of life (see section 3.2). The committee agreed that, if idebenone were recommended, the recommendation would not restrict access for some

people over others. No other equality or social value judgement issues were identified.

Innovation

3.22 The clinical experts that that idebenone is innovative for treating LHON in people with a very high unmet need. They also thought that idebenone is a step change for LHON treatment because it has the potential to make a difference in health-related quality of life. They explained that, with idebenone, about 50% of people will have the opportunity of a better visual outcome. The committee acknowledged the benefits offered by idebenone and heard from the clinical and patient experts that idebenone could offer wide-ranging effects including:

- reduced anxiety and depression
- independence with daily activities
- increased socialising
- improved mental health
- rebuilding confidence
- better education and career opportunities.

The committee thought that the uncertainties in the evidence meant that it was unclear whether these had been fully captured in the model. It concluded that it had not been presented with evidence of any additional benefits specific to idebenone that had not been captured in the QALY measurement.

Conclusion

Recommendation

3.23 The committee took into account its preferred assumptions, key uncertainties in the model and the other factors in its decision making. Taking these into account, the ICERs based on assumptions were higher than what NICE normally considers a cost-effective use of NHS resources It concluded that the most plausible ICER for idebenone compared with

standard care was considerably above its preferred ICER threshold. So, idebenone is not recommended.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Richard Nicholas
Chair, technology appraisal committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Harsimran Sarpal
Technical lead

Eleanor Donegan

Adam Brooke
Technical advisers

Vonda Murray

Kate Moore

Project managers

Linda Landells

Ross Dent

Associate directors

ISBN: [to be added at publication]

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 23 May 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Chiesi Ltd

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NICE National Institute for Health and Care Excellence

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not Applicable.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Executive Summary	**Summary:** Chiesi has carefully considered the committee's assessment of the evidence submitted for idebenone as a treatment for Leber's hereditary optic neuropathy (LHON) in patients aged 12 and above and would like to thank the National Institute for Health and Care Excellence (NICE) for the opportunity to comment on the second Draft Guidance Consultation (DGC2) document issued on February 2025. The company is disappointed by the draft recommendation not to recommend idebenone and is eager to work in partnership with NICE and National Health Service (NHS) England to find a solution that enables access to idebenone for patients with LHON aged 12 years and over. There is a high unmet need for a treatment for LHON as the current standard of care (SoC), consisting of lifestyle management, genetic counselling and symptomatic treatments, does not prevent vision loss or allow recovery of visual function. Idebenone is the first and only licensed treatment option with evidenced improvement in visual impairment in adolescents and adults with LHON. Therefore, the company kindly requests that the committee reconsiders the second negative draft recommendation to enable timely access to this clinically effective treatment. To support the External Assessment Group (EAG) and committee in their decision-making, the company has provided an updated integrated analysis incorporating all available clinical data

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	(including the RHODOS data), to inform the treatment effect of idebenone and SoC treatments. Results of this analysis have been incorporated into the cost-effectiveness model. This analysis, as well as any assumptions within the model, has been externally validated by UK clinicians. Additionally, the company has revised their base-case [redacted]. The company's revised base-case incremental cost-effectiveness ratio (ICER) is £28,241 per quality-adjusted life year (QALY). **Key updates in this response to ensure appropriate committee decision-making:** • **Inclusion of the RHODOS data in the propensity score weighted analysis (PSWA) of the integrated analysis from baseline to 6 months.** To address concerns raised by both the EAG and NICE regarding the validity of excluding RHODOS from the integrated analysis and the naïve merging of the RHODOS RCT population with the integrated analysis the company has re-run the PSWA using the integrated analysis, including RHODOS at month 6, from baseline. The updated integrated analysis includes all available clinical data (RHODOS, RHODOS-OFU, EAP, CaRS-I, CaRS-II, LEROS and PAROS) for both idebenone and SoC. One single weight was calculated for the full ITT population of the integrated analysis, from baseline through to month 48. For more details on the integrated analysis, please see company's response to Issue 1 in this response document. • **Clinical validation:** To validate the findings of the updated integrated analysis and obtain validation of the company's base-case assumptions, the company conducted a clinical validation on April 24th, 2025. The outcomes of the updated integrated analysis set, including Best Corrected Visual Acuity, were presented to clinicians. The company's base-case assumptions regarding Time to Indication for Treatment Discontinuation and maintenance of treatment benefit after treatment discontinuation were discussed. For more details on the Time to Indication for Treatment Discontinuation and maintenance of treatment benefit after treatment, please see company's response to Issue 2 in this response document. • **Update of the cost-effectiveness model:** Clinical efficacy from the updated integrated analysis was incorporated in the cost-effectiveness model. Additionally, some assumptions were revised based on the second appraisal committee meeting (ACM2) discussion, DGC2 and the clinical validation. • [redacted]. [redacted], idebenone is a cost-effective use of NHS resources for the treatment of a rare disease in an underserved population with a high unmet need. For more information, see the cost-effectiveness results in **Table 10** of this DGC2 response.
1.Including RHODOS	**<u>The company, EAG and committee's approaches at ACM2:</u>** As part of the company's response to NICE's first draft guidance, an integrated analysis dataset was created, incorporating all available clinical data (RHODOS, RHODOS-OFU, EAP, CaRS-I,

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in the PSWA of the integrated analysis & Baseline distributio n	CaRS-II, LEROS and PAROS) for both idebenone and SoC.[1] To ensure comparability between the idebenone and SoC treatment arms, the company conducted a propensity score weighted analysis (PSWA) using the integrated analysis dataset. Given the availability of RHODOS data, a double-blind placebo controlled RCT, from baseline to 6 months, transition probabilities were derived solely from RHODOS for this period. The PSWA was then used to derive transition probabilities from month 6 onwards. However, the EAG raised concerns about the "*mismatch between the populations informing the 6-month data and subsequent follow-up data*."[2] The committee questioned the validity of excluding RHODOS from the integrated analysis. The EAG and the committee also noted they would have preferred to see one consistent population used in the model throughout the time horizon. **To aid in this response, the company has integrated the data from the RHODOS trial into the PSWA** To meet the request from the EAG and the committee, the company have re-run the PSWA using the integrated analysis from baseline, now incorporating RHODOS into this weighted analysis. The propensity score weighting ensures an unbiased comparison between treatment groups, by adjusting for differences in baseline characteristic, which creates more reliable estimates of treatment effects. One weight was calculated for the full ITT population of the integrated analysis, from baseline through to month 48. Data of 1,252 patients from all studies were included in the integrated analysis datasets. Of these, 847 patients were included in the ITT population and 405 were excluded. Of the patients included in the ITT population, 409 were analysed for the PSWA in the idebenone treatment group and 438 for the SoC treatment group, creating the biggest possible sample size available for the analysis. **Propensity score weighting analysis** The propensity score (PS) model was run considering the following as regression factors: gender, age at onset, time from onset at baseline, baseline best BCVA, unilateral/bilateral involvement at baseline and type of mutation. Patients with missing information on these baseline variables have been excluded in running the model (1 SoC patient only, due to missing age at onset.). For more detail on this please refer to the Integrated Analysis Statistical Report (provided as part of the ACD1 responses).[3] As reported in the natural history (NH) data, after the onset, the disease progression is expected to be characterised by a quick deterioration until nadir followed by a slow stabilisation with some cases of spontaneous improvement. For this reason, the assumption of linearity cannot be made in the first months after baseline and therefore, only a weighted analysis was considered for the analysis-visits from baseline to month 12. The summaries of the propensity score weights applied to the full ITT population at baseline are presented in Table 14, Appendix A. **Multiple imputation** To address missing data in the efficacy analyses performed from 12 months onwards, a multiple imputation (MI) approach was used to assign a value to incomplete cases. MI replaces each missing value with a set of plausible values that represent the uncertainty about the true imputed value. The multiple imputed datasets were then analysed using standard procedures for complete data, and the results from these analyses were combined.

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Two different approaches were used for the imputation, based on different assumptions: Missing At Random (MAR) and Missing Not At Random (MNAR). No imputation was performed for the analysis of best BCVA before 12 months analysis visit.

- **MAR**: In MAR, multiple imputations assume that the data are missing at random, meaning that, the probability that an observation is missing depends only on the observed values of other variables, not on unobserved values.

- **MNAR**: In MNAR, a pattern-mixture model is used to estimate the distribution of responses as a mixture of observed and missing responses. A control-based pattern imputation is applied, assuming that patients who withdraw from idebenone treatment will have an efficacy trajectory similar to those in the standard-of-care treatment group.

There is no standard test whether the data is MAR or MNAR - there are many references in the literature that highlight that any test that might be conducted would not be conclusive - therefore no test was conducted. For more details on the statistical methods used please refer to the SAP and the integrated analysis statistical report attached as part of this response.[3,4]

Mixed model for repeated measures
The relative effectiveness of idebenone vs SoC was analysed based on the change from baseline in best BCVA using a MMRM. An adjusted estimate of the mean change from baseline in best BCVA was derived for each visit. The results from the MMRM analysis were adjusted for sex, age at onset, mutation, time since onset, and baseline best BCVA. The model was run on all ITT patients after month 12. The MMRM analysis has an implicit imputation of missing values under a MAR assumption and this model has been used to present the below results. However, as a sensitivity analysis, the above model was rerun on the imputed datasets as per MNAR approach described above, which was the preferred approach by the EAG as it was considered to be the least biased.[2]

Results of the updated PSWA:
Baseline characteristic
The baseline characteristics of patients are derived from the integrated analysis (including RHODOS), weighted, and are presented in Table 1.

The weighted analysis has been conducted on the ITT population of the integrated analysis from baseline, however, patients from RHODOS are only followed up for 6 months and a multiple imputation approach is not conducted until month 12 onwards. Therefore, the sample size of the population changes whilst still applying the same treatment arms weights used at baseline. For this reason, the weighted characteristics have also been presented at 6 and 12 months in Table 15 and Table 16, Appendix B. As demonstrated, the characteristics remain appropriately weighted across treatment arms after baseline to month 12.

From month 12 onwards, multiple imputation has been applied, therefore patients with missing data have not been excluded from the patient sample but included with imputed data. Hence, the distribution of the baseline characteristics in each treatment arm remains the same as it was at month 12. As the baseline characteristics are well balanced at month 12 and do not change from that timepoint, they remain well balanced across the model time horizon. Therefore, the weighted baseline characteristics have only been presented up until month 12.

Table 1: Baseline characteristics from the integrated analysis, weighted

Parameter		Idebenone	SoC
Gender	Male, (%)	[redacted]	[redacted]
	Female, (%)	[redacted]	[redacted]

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Mutation	**G11778A**	[redacted]	[redacted]
	G3460A	[redacted]	[redacted]
	T14484C	[redacted]	[redacted]
	Other	[redacted]	[redacted]
Laterality	**Bilateral**	[redacted]	[redacted]
	Unilateral	[redacted]	[redacted]
Analysis age (at first onset), mean (SD)		[redacted]	[redacted]
Time from first onset at baseline (months), mean (SD)		[redacted]	[redacted]
Baseline best visual improvement (LogMar), mean (SD)		[redacted]	[redacted]

Abbreviations: LogMAR – Logarithm of the minimum angle of resolution; SD – standard deviation; SoC – standard of care

The baseline characteristics from the integrated analysis were presented to two clinicians in validation meetings held on 24th April 2025. One clinician stated they agreed that the data were representative of what is typically seen in clinical practice, specifically noting that the proportion of G11778A mutations was approximately 60%. The other clinician agreed that as awareness of LHON improves, they would expect to see the patient distribution to be aligned to that observed in the integrated analysis.

Baseline distribution – weighted

The baseline distribution of the new integrated analysis (including RHODOS), weighted, is presented in Table 2. The baseline distribution from the updated weighted analysis was further validated by clinicians in a clinician validation meeting (April 2025) where clinicians stated that "*the distribution of patients in the RHODOS trial was skewed towards more chronic patients and that they would expect to see patients sooner and anticipate to see a lower percentage of patients with worse logMAR compared to the ones presented for the RHODOS trial*" and that "*the integrated analysis baseline distribution provides a more realistic representation of clinical practise"*.[5]

Table 2: Baseline distribution – Weighted analysis

	LogMAR < 0.3	0.3 ≤ LogMAR <0.6	0.6 ≤ LogMAR < 1.0	1.0 ≤ LogMAR < 1.3	1.3 ≤ LogMAR < 1.7	CF	HM	LP	Total
Idebenone (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CF – Counting fingers; HM – Hand motion; LogMAR – Logarithm of the minimum angle of resolution; LP – Light perception; SoC – Standard of care

Change from baseline in best BCVA as measured by MMRM

The relative effectiveness of idebenone vs. SoC was analysed in terms of change from baseline in best BCVA using a MMRM, ran with both an implicit imputation of missing values under MAR and MNAR assumptions. The MMRM analysis produced estimates for 6-month intervals from month 12 to month 48. The MMRM model included treatment group, analysis visit, treatment-by-analysis-visit

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interaction, gender, LHON mtDNA mutation, time from onset at baseline, best BCVA at baseline, as fixed effects, and the baseline best BCVA-by-analysis-visit interaction and it was weighted by the stabilised inverse probability of treatment weights computed by the PS model. The results of the analysis were supportive of the clear clinical benefit of idebenone over SoC.

The estimated change from baseline in best BCVA in LogMAR and the estimated difference in best BCVA in LogMAR for idebenone and SoC from baseline using MAR and MNAR assumptions are presented in Table 4 and Table 5, respectively. Table 3 presents the change in best BCVA in LogMAR derived from the weighted MMRM. A visual representation of Table 4 and Table 5 are provided below, in Figure 1 and Figure 2.

Table 3: Change in best BCVA in LogMAR derived from the integrated analysis as measured by a MMRM analysis – weighted

Analysis visit	Estimated change from baseline in LogMAR ± SE (95% CI)		Estimated difference in LogMAR	P-value
	Idebenone	SoC	Idebenone vs SoC	
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]
Month 30	[redacted]	[redacted]	[redacted]	[redacted]
Month 36	[redacted]	[redacted]	[redacted]	[redacted]
Month 42	[redacted]	[redacted]	[redacted]	[redacted]
Month 48	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA – Best correction visual acuity; CI – Confidence interval; LogMAR – Logarithm of the minimum angle of resolution; MAR – Missing at random; MMRM – Mixed models for repeated measure; SE – Standard error; SoC – Standard of care

Table 4: Change in best BCVA in LogMAR derived from the integrated analysis as measured by a MMRM analysis – MAR

Analysis visit	Estimated change from baseline in LogMAR ± SE (95% CI)		Estimated difference in LogMAR	P-value
	Idebenone	SoC	Idebenone vs SoC	
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]
Month 30	[redacted]	[redacted]	[redacted]	[redacted]

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Month 36		[redacted]			[redacted]		[redacted]	[redacted]
Month 42							[redacted]	[redacted]
Month 48							[redacted]	[redacted]

Abbreviations: BCVA – Best correction visual acuity; CI – Confidence interval; LogMAR – Logarithm of the minimum angle of resolution; MAR – Missing at random; MMRM – Mixed models for repeated measure; SE – Standard error; SoC – Standard of care

Table 5: Change in best BCVA in LogMAR derived from the integrated analysis as measured by a MMRM analysis – MNAR

Analysis visit	Estimated change from baseline in LogMAR ± SE (95% CI)						Estimated difference in LogMAR	P-value
	Idebenone			SoC			Idebenone vs SoC	
Month 12		[redacted]			[redacted]		[redacted]	[redacted]
Month 18							[redacted]	[redacted]
Month 24							[redacted]	[redacted]
Month 30							[redacted]	[redacted]
Month 36							[redacted]	[redacted]
Month 42							[redacted]	[redacted]
Month 48							[redacted]	[redacted]

Abbreviations: BCVA – Best corrected visual acuity; CI – Confidence interval; LogMAR – Logarithm of the minimum angle of resolution; MMRM – Mixed models for repeated measure; MNAR – Missing not at random; SE – Standard error; SoC – Standard of care

Figure 1: Change in best BCVA in LogMAR derived from the integrated analysis as measured by a MMRM analysis - MAR

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Abbreviations: BCVA – Best corrected visual acuity; LogMAR – Logarithm of the minimum angle of resolution; MAR – Missing at random; MMRM – Mixed models for repeated measure; SoC – Standard of care

Figure 2: Change in best BCVA in LogMAR derived from the integrated analysis as measured by a MMRM analysis – MNAR

Abbreviations: BCVA – Best corrected visual acuity; LogMAR – Logarithm of the minimum angle of resolution; MMRM – Mixed models for repeated measure; MNAR – Missing not at random; SoC – Standard of care

As presented in Table 4, Table 5, Figure 1, and Figure 2:

- **At month 12**, there is an estimated mean worsening with a change from baseline LogMAR of [redacted] for the MAR (MNAR) assumption for the idebenone group and [redacted] for the MAR (MNAR) assumption for the SoC group. The difference between

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treatment groups is a LogMAR of [redacted] ([redacted]) from the MAR (MNAR) assumptions respectively, translating to a further improvement of ~[redacted] letters, which is statistically significant ([redacted]) in favour of idebenone.

- Similar results are observed at **month 18**, with a difference between treatment groups of LogMAR [redacted] ([redacted]) under a MAR (MNAR) assumption, equivalent to ~[redacted] letters, which is statistically significant ([redacted]) in favour of idebenone.

- At **month 24**, the estimated mean change vs baseline in SoC patients decreases slightly but the difference between treatment groups remains statistically significant ([redacted]) in favour of idebenone with a difference of [redacted] ([redacted]) under a MAR (MNAR) assumption.

- At **month 36**, the estimated mean change vs baselines in SoC patients decreases slightly, likely due to the spontaneous recovery observed in some patients in the SoC arm, but the difference between the treatment groups are still statistically significant ([redacted]). The difference is still in favour of idebenone with a logMAR difference of [redacted] ([redacted]) under a MAR (MNAR) assumption.

Although not used in the economic model, the company has also provided the estimated change in LogMAR and estimated difference in LogMAR for month 42 and month 48. Data from the integrated analysis for months 42 and 48 were not used due to small sample size (with only 30 patients in the idebenone arm and 32 in the SoC arm at month 42). The sample size decreases significantly after month 36, therefore no data post month 36 was used in the economic model. For further details on the number of patients missing at each timepoint for which data was imputed for see Appendix D. The data also demonstrates a statistically significant difference between the idebenone and SoC arm in the long-term and shows how patients treated with idebenone continue to see a clinical benefit compared to SoC.

Achievement of clinically relevant benefit

Clinically relevant benefit (CRB) was analysed using a logistic regression model, weighted by stabilised inverse probability of treatment weights, using a logit link function and was run on all ITT patients of the integrated analysis.

The CRB in the best- seeing eye is also evident in the analysis, with patients treated with idebenone more likely to achieve a CRB compared to SoC patients. Table 6 presents the odds ratio at each time point for the CRB of idebenone versus SoC.

At month 12, patients on idebenone are almost 3 times more likely to have a CRB compared to the SoC patients, with an odds ratio of [redacted]. The result is statistically significant. For all the remaining timepoints in the analysis, the odds ratio [redacted], without losing statistical and clinical significance.

Table 6: Odds ratio of the CRB of patients' treatment with idebenone compared to SoC from the integrated analysis as measured using a weighted logistic model

Analysis visit	Idebenone vs SoC		
	Odds ratio	Odds 95% CI	Odds ratio p-value
MAR			
Month 12	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]
Month 30	[redacted]	[redacted]	[redacted]
Month 36	[redacted]	[redacted]	[redacted]

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Month 42		[redacted]			[redacted]			[redacted]	
Month 48		[redacted]			[redacted]			[redacted]	
MNAR									
Month 12		[redacted]			[redacted]			[redacted]	
Month 18		[redacted]			[redacted]			[redacted]	
Month 24		[redacted]			[redacted]			[redacted]	
Month 30		[redacted]			[redacted]			[redacted]	
Month 36		[redacted]			[redacted]			[redacted]	
Month 42		[redacted]			[redacted]			[redacted]	
Month 48		[redacted]			[redacted]			[redacted]	

Abbreviations: CI – Confidence interval; CRB – Clinically relevant benefit, SoC – Standard of care; MAR – Missing at random; MNAR – Missing not at random

Approaches explored to derive transition probabilities used in the economic model

Transition probabilities for both treatment arms were derived from the updated analysis including RHODOS, produced from the integrated analysis set.

From baseline to month 12, transition probabilities are based on weighted observations obtained from the integrated analysis, based on stabilised inverse probability of treatment weights, with no imputations done.

For transition probabilities from month 12 to month 36, the analysis includes ITT patients with at least one assessment on the month 12 analysis visit and after. A PS model has been run to estimate a stabilised inverse probability of treatment weight which considers baseline variables of all ITT patients with all baseline variables available at baseline. A single stabilised weight for all ITT patients was applied and used consistently across all transitions from month 12 onward. The approaches used to estimate transition probabilities explored in the model include the following:

1. **MAR**: For each imputed dataset under the MAR assumption, each transition probability has been estimated along with its SE by a logistic regression model. A FIRTH penalised maximum likelihood estimation was applied to avoid complete separation of data and reduce bias in the parameter estimates. The model is weighted by stabilised inverse probability of treatment weights and includes the treatment group as the only factor.

2. **MNAR**: The approaches under point 1 was repeated under the MNAR assumption.

The use of the integrated analysis to inform the baseline distribution:
In the base case in ACM2, the integrated analysis (including RHODOS) is used to populate the baseline distribution as this is reflective of clinical practice and uses the largest possible sample size.

The EAG previously criticised the use of the integrated analysis ITT population (including RHODOS) as the baseline distribution because the EAG was concerned about the mismatch between the data sources used to inform the baseline distribution and those used to inform the transition probabilities in the first 6 months. However, with the inclusion of RHODOS data in the weighted analysis from baseline, it is now appropriate to use the baseline distribution from the ITT population of the integrated analysis (with RHODOS) to ensure that the baseline distribution and transition probabilities are informed by a consistent data source. Therefore, the baseline distribution has now been derived from the updated weighted analysis, as presented in Table 2, and has been incorporated into the model base-case.

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Using the whole ITT patient population from the integrated analysis (including RHODOS), weighted, ensures that the data source of baseline distribution of patients is in line with the data used to inform the transition probabilities from baseline. The integrated analysis is used to populate the baseline distribution as this is reflective of clinical practice and uses the largest possible sample size. Using natural history data to establish the baseline is consistent with the NICE RWE Framework's emphasis on leveraging high-quality real-world data sources to inform clinical decision-making.[6]

The use of the integrated analysis baseline distribution in the model was also validated through two separate clinical validation meetings held on October 17th, 2024, and April 24th, 2025.[5,7] Notably, one clinician commented during the October 17th meeting that "*The baseline cannot be disputed given its basis in a large dataset*." Similarly, another clinician stated at the April 24th meeting that "*The integrated analysis baseline distribution provides a more realistic representation of clinical practice*" (please see Appendix C: Clinician validation interview for further details).[5]

The model accurately predicts outcomes from the integrated analysis:
As demonstrated in Table 7 and Table 8, the outputs of the economic model using the various transition probabilities are all similar to the clinical outputs obtained from the integrated analysis set. This is also visually presented in Figure 3 and Figure 4 for the MAR and MNAR approaches respectively. The values for month 6 were derived from the weighted analysis transition probabilities, with no imputations, therefore the mean change in BCVA in baseline at month 6 is the same across the MAR and MNAR assumptions. As can be seen in both figures the model accurately predicts the change in logMAR from baseline using both the MAR and MNAR modelling approaches. The transition probabilities from the updated integrated analysis are able to predict the outputs from the clinical data even more accurately than those presented at ACM2.

Table 7: Mean change in BCVA from baseline – idebenone

	Mean change in BCVA from baseline – weighted integrated analysis with logistic model MAR		**Mean change in BCVA from baseline – weighted integrated analysis with logistic model MNAR**	
Month	**Economic model**	**Integrated analysis dataset**	**Economic model**	**Integrated analysis dataset**
Baseline	-	-	-	-
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]
Month 36	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA – Best corrected visual acuity; MAR – Missing at random; MNAR – Missing not at random

As demonstrated in Table 7, the two approaches of deriving transition probabilities for idebenone produce similar outputs at each timepoint, with slight difference of approximately LogMAR [redacted] (equivalent to [redacted]) at month 6 when comparing the economic model to the outputs from the integrated analysis using a MAR or MNAR assumption. At month 12, 18, 24 and 36 when comparing the outputs of the model with the outputs from the integrated analysis for both MAR and MNAR a difference of less than or equal to LogMAR [redacted] (equivalent to about [redacted]) is observed.

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Table 8: Mean change in BCVA from baseline – SoC

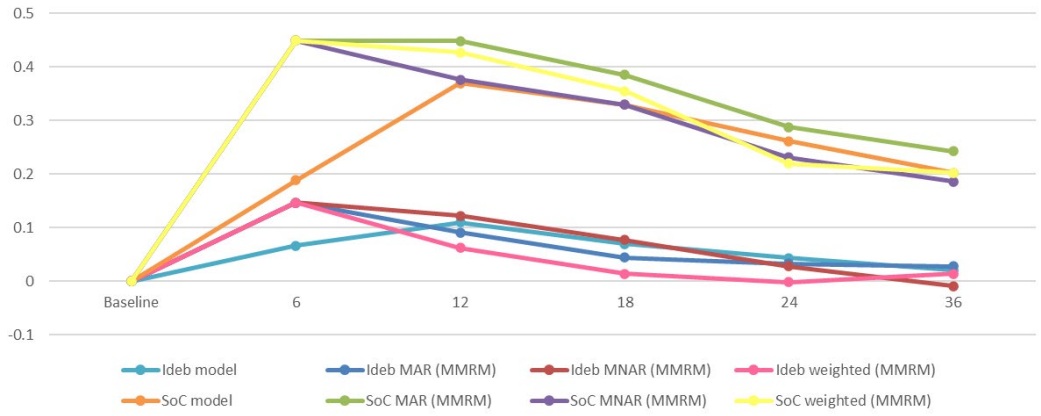
	Mean change in BCVA from baseline – weighted integrated analysis with logistic model MAR		Mean change in BCVA from baseline – weighted integrated analysis with logistic model MNAR	
Month	**Economic model**	**Integrated analysis dataset**	**Economic model**	**Integrated analysis dataset**
Baseline	-	-	-	-
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]
Month 36	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA – Best corrected visual acuity; MAR – Missing at random; MNAR – Missing not at random; SoC – Standard of care

As demonstrated in Table 8, the two approaches of deriving transition probabilities for SoC produce similar outputs at each timepoint. The biggest variation when comparing the economic model outputs and those from the integrated analysis being when using the MAR assumption at month 6 with a difference of approximately LogMAR [redacted] (equivalent to [redacted]). At months 12, 18, 24, and 36 a difference of less than or equal to LogMAR [redacted] (equivalent to about [redacted]) is observed when comparing the outcomes of the economic model to those of the integrated analysis using a MAR or MNAR assumption.

The discrepancy at month 6 for the SoC arm can be attributed to the half-cycle correction applied in the economic model. The half-cycle correction (HCC) is a methodological adjustment that takes the average of the current cycle population and the subsequent model cycle, aiming to reduce biases associated with using a 3-month cycle, or in this case, 6-monthly data. This is further explored in a scenario presented in Figure 5 and Figure 6.

Figure 3: Change in logMAR from baseline – MAR



Abbreviations: ideb – idebenone; MAR – Missing at random; MNAR – Missing not at random; MMRM – Mixed model of repeated measures; SoC – Standard of care

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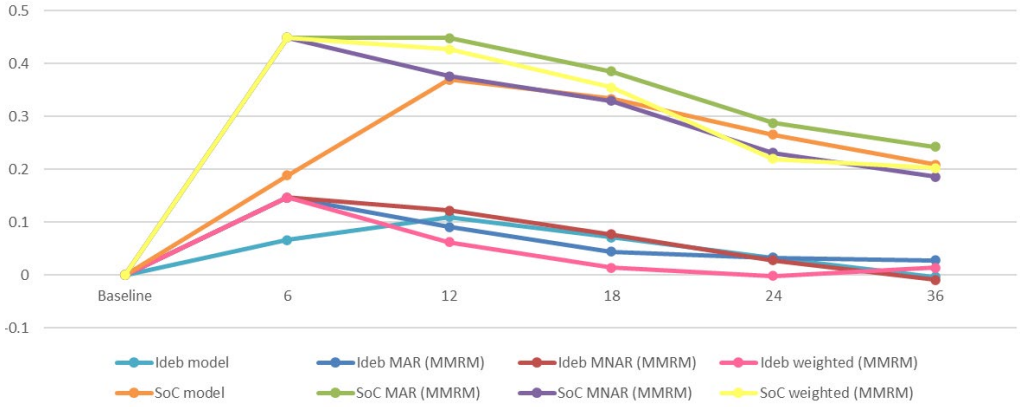
Figure 4: Change in logMAR from baseline – MNAR



Abbreviations: ideb – idebenone; MAR – Missing at random; MNAR – Missing not at random; MMRM – Mixed model of repeated measures; SoC – Standard of care

To validate the outputs from the model using the transition probabilities derived from the integrated analysis as clinically plausible outcomes (as presented in Table 4 and Table 5), the company presented the difference in the mean change in BCVA of idebenone and SoC as derived from the integrated analysis alongside the outputs from the economic model to clinicians during a clinician validation interview conducted on the 24th April 2025 (please see Appendix C for further details on the validations). Both clinicians interviewed agreed that for the idebenone arm the outputs from the company's economic model were not significantly different from the outcomes from the integrated analysis, with one clinician stating that "*a difference of logMAR 0.080 (approximately 4 letters) at month 6 to be neither significant nor meaningful".* The clinician further noted that, "*at this stage, patients may still be stabilizing, making it too early to attribute any observed improvement to a therapeutic effect"* and that "*the data at month 6 may be influenced by several factors, such as the timing of onset and the time elapsed since diagnosis and the skewing of the data may be less skewed over time, resulting in more consistent findings*."(please see Appendix C: Clinician validation interview for further details).[5]

HCC scenario:

As stated above the model accurately predicts the outputs from the integrated analysis set, except for month 6 in the SoC arms. This is driven by the application of the half-cycle correction in the model. There is a large swing in the proportion of patients in each health state from baseline to month 6. For example, in the SoC arm at baseline there are 232 patients that start in logMAR <0.3 health state and 122 that start in the logMAR 0.6-1.0, after the first transition this results in 68 patients in logMAR<0.3 and 66 patients in logMAR 0.6-1.0 at month 6. However, applying the HCC results in 150 patients in logMAR <0.3 and 94 patients in logMAR 0.6-1.0 which drives the difference in the mean change in logMAR at month 6.

To demonstrate this, the company have run scenarios (MAR and MNAR) excluding the HCC assumption completely. In this scenario the model is able to very accurately predict the outcomes from the integrated analysis, as shown in Figure 5 and Figure 6. The difference for the SoC arm between the model and the outputs from the integrated analysis a 0.071 at month 6. The company spoke to two clinicians on 24th April 2025 to validate how accurately the economic model can predict the outcomes from the integrated analysis. Both clinicians stated that this difference in logMAR at month 6 of approximately 4 letters as *"not significantly different"*.[5]

Figure 5: Change in logMAR from baseline without half cycle correction – MAR

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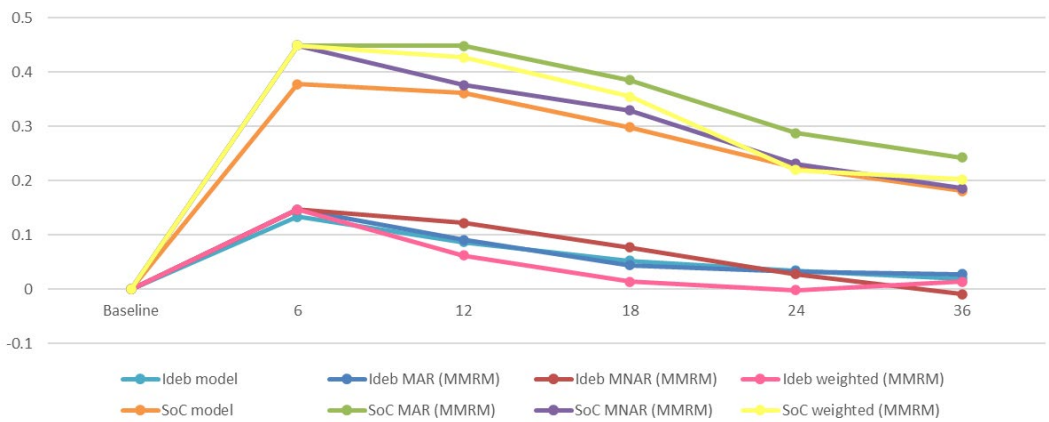
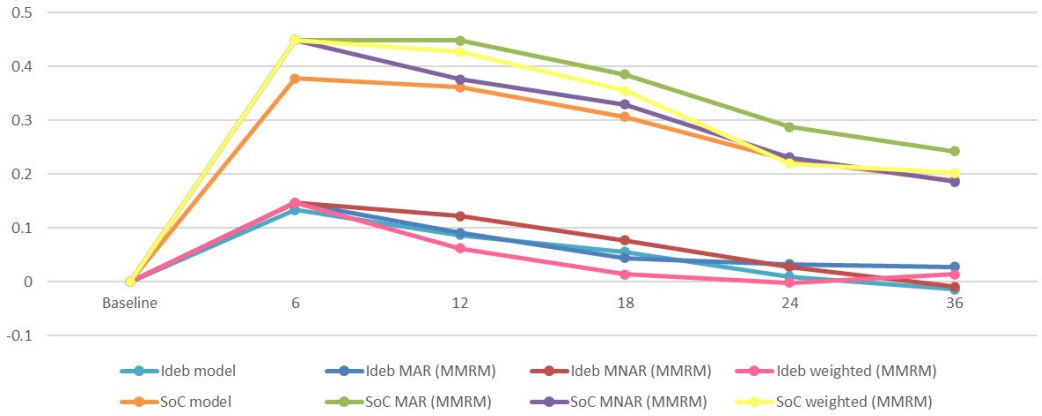


Abbreviations: ideb – idebenone; MAR – Missing at random; MNAR – Missing not at random; MMRM – Mixed model of repeated measures; SoC – Standard of care

Figure 6: Change in logMAR from baseline without half cycle correction – MNAR



Abbreviations: ideb – idebenone; MAR – Missing at random; MNAR – Missing not at random; MMRM – Mixed model of repeated measures; SoC – Standard of care

The company maintains that the outcomes of the model are reflective of the outcomes of the weighted analysis and maintain the use of the HCC in the base case analysis.

Revised company base case:

The assumption of using a logistic model with a data MAR assumption was criticized by the EAG. The EAG stated that they thought the MAR approach was taken by the company "*with no robust justification for the choice of the approach*". The EAG preferred the MNAR approach as they consider this to be less biased.[2] As demonstrated in Figure 3 and Figure 4, the transition probabilities derived using the MNAR assumption provide more accurate estimates to outputs of the integrated analysis.

SoC patients do dot typically attend appointments once their vision has deteriorated and there is no available treatment. This is confirmed in published literature – "patients living with Inherited Retinal Degenerations (IRDs) may not regularly visit eye clinics as they are often told that 'nothing can be done".[8] The RWE SoC data informing the integrated analysis, was collected at the point a patient attends the clinic. An increased proportion of patients with improved VA can therefore be seen in the SoC arm of the integrated analysis at later dates, as the SoC patients with worse VA are less likely to have attended their appointment. This leads to informative censoring in favour of SoC.

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	While there is no formal test to validate the use of the MAR versus MNAR assumption, the fact that the MNAR assumption provides more accurate results confirms that there is likely informative censoring in favour of SoC. Therefore, the company have updated the base-case to use the transition probabilities derived from the logistic model using the MNAR assumption from month 12 onwards. With the updated PS weighted analysis including RHODOS and using one population with the same weight across the time horizon, the company has adopted the following approaches for informing transition probabilities in the updated base-case: • **Baseline distribution:** Integrated analysis (including RHODOS), weighted • **Baseline – month 12**: Transition probabilities are derived from the new integrated analysis (including RHODOS and using one population weight) and PS weighted based on stabilised inverse probability of treatment weights. • **Month 12 – month 36**: Transition probabilities are derived from the integrated analysis, PS weighted and estimated using a logistic regression model with the MNAR. • **Month 36 onwards**: As previously modelled, no further movement is assumed for patients after month 36. Data from the integrated analysis for months 42 and 48 were not used due to small sample size. Updating the base case assumptions to use the MNAR assumption, with the updated weighted baseline distribution (Table 2) and weighted baseline characteristics (Table 1), results in an updated base case ICER of £28,241. All updates to the company's base case analysis along with scenarios can be found in Table 9. As a scenario the company also ran the model results without the HCC, this scenario has minimal impact on the ICER and excluding the HCC results in an ICER of £33,634 and £28,136 for the MAR and MNAR assumptions, respectively. To conclude, the use of the updated weighted analysis (including RHODOS), using one weight and one single population from baseline, to inform the clinical effectiveness and baseline distribution of idebenone and SoC ensures all available data are used within the CEA and allows the value of idebenone to be accurately reflected. The updates to the weighted analysis, including applying it from baseline and aligning it to the baseline distribution used, also addresses the EAG's concerns of differing populations at different timepoints and the uncertainty of the model outcomes.
2. Time on treatment	**Time on treatment within the economic model is informed by a time-to-treatment discontinuation indicator obtained from the integrated analysis. The company remains confident that time to indication to treatment discontinuation Kaplan-Meier (KM) estimates from the integrated analysis is the most appropriate source to inform treatment duration for patients receiving idebenone, as it accurately reflects the duration of treatment clinicians would expect to see in clinical practice. To further support the model's alignment with real-world clinical expectations, the company has incorporated functionality to account for patients who may continue to show improvement in VA beyond 36 months, indicating that a small proportion of patients would remain on treatment beyond this point.** **<u>Company base-case and EAG preferences</u>** At ACM2, the modelling of treatment duration within the CEA was informed using the time to indication to treatment discontinuation KM estimates presented in Figure 7 which showed treatment

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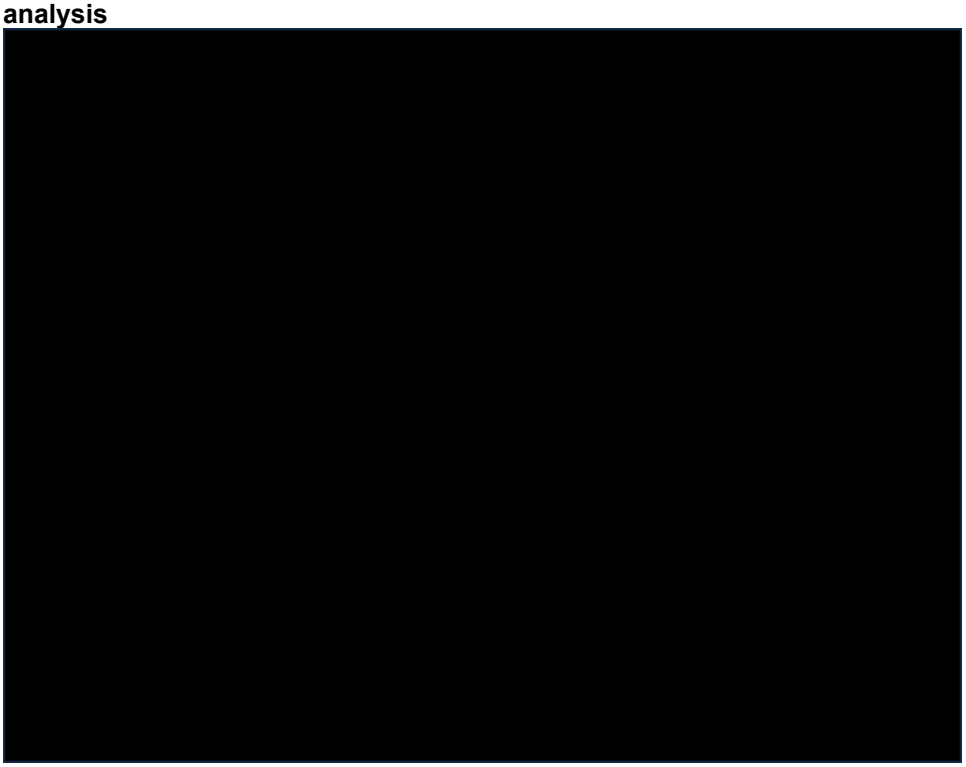
duration of up to 54 months. The KM estimates presented in Figure 7 were also shared as part of the company clinician validation meeting (17th October 2024, Appendix D), where both clinicians agreed that the curve provided reasonable estimates of the duration of treatment in clinical practice and agreed that most patients would end treatment by month 36.[7] As demonstrated in the KM curve and used as a proxy for persistence in the economic model, it is assumed that [redacted] of patients are still on treatment at month 12, [redacted] of patients are still on treatment at month 24, [redacted] of patients are still on treatment at month 36 and all patients are off treatment by month 54.

The EAG considers that the time to discontinuation from the integrated analysis to be more clinically reflective of patient time on treatment as it presents when patients discontinued treatment, not when patients should have discontinued treatment according to the expert clinicians advising the company. However, it is important to highlight that the progression of LHON and the therapeutic effects of idebenone are now better understood. With growing clinical experience and a deeper knowledge of the disease and treatment mechanisms, clinicians are now better positioned to determine the appropriate duration of idebenone therapy, making expert clinical judgement a more relevant guide to how idebenone will be administered once it becomes available.

Figure 7: Time to indication to treatment discontinuation estimated using the integrated analysis



Abbreviations: Prob. – probability; Trt – Treatment

The company wishes to reiterate that the time on treatment data from the integrated analysis includes treatment duration data from the EAP study, which is not reflective of how idebenone would be used in the clinical practice. The EAP study is of non-controlled and open-label nature. Within the study, there was a non-uniform duration of treatment where the treatment duration was

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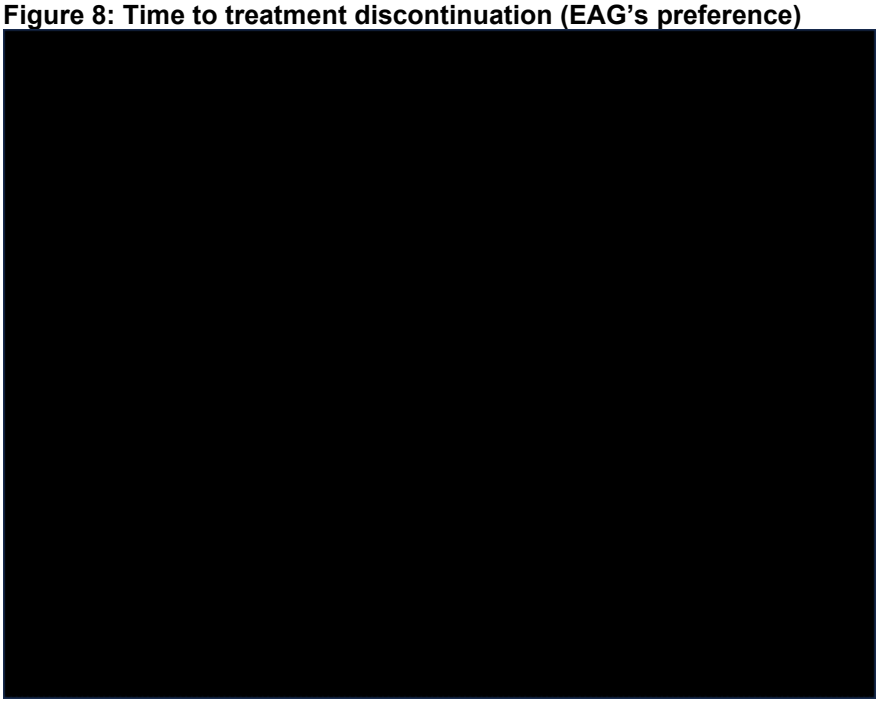
not predetermined but left at the treating physician's discretion, with a deliberately broad range of treatment duration permitted. At the onset of the EAP study, knowledge about LHON progression over time and the best duration of treatment was limited. This has led to varying lengths of treatment duration within the EAP where the treatment duration for the efficacy population in the EAP study ranged from 2.4 to 70.4 months. This variability, particularly the extended treatment durations observed in the EAP, primarily drives the longer time on treatment seen in the EAG's preferred time to discontinuation KM curve. The EAG's KM curve based on time to discontinuation as seen in Figure 8 shows approximately [redacted] of patients still on treatment at month 36 and approximately [redacted] of patients still on treatment at month 108 (9 years). The EAG's assumption that patients would remain on treatment for up to approximately 9 years, based on time to idebenone discontinuation, is an excessive overestimation and contrary to expert clinician opinion that the majority of patients would be on treatment for no more than 3 years.

Figure 8: Time to treatment discontinuation (EAG's preference)



Abbreviations: Prob. – probability; Trt - Treatment

<u>Treatment guidelines formed from company and clinician discussions</u>

The company would like to reiterate that the understanding of the treatment of LHON with idebenone has developed significantly in recent years. The uncertainty of the required idebenone treatment duration, following the short 6-month treatment duration of RHODOS, led to an over-compensation in length of treatment duration in the subsequent EAP study. However, evidence from the LEROS study, alongside the integrated analysis of all idebenone data and clinical expert opinion demonstrates that these prolonged treatment durations seen in the EAP study were excessive, and that the vast majority of patients benefit from treatment over a period of 2 to 3 years of treatment.

LHON patients typically follow one of two possible VA trajectory patterns;

1. Their VA deteriorates to nadir and remains at this VA level
2. Their VA deteriorates to nadir and then improves before levelling out at a new VA plateau.

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	Combining these patterns with the time to indication of treatment discontinuation graph incorporated by the company in the base-case analysis (Figure 7), patients can be categorised into 4 broad categories: • **Fast responders**: patients may respond, plateau and be off treatment before 2 years. • **Standard responders**: the vast majority of patients will be treated for 2-3 years before reaching a plateau. • **Slow responders**: in very rare cases, less than 1%, a patient may be showing consistent signs of VA improvement until they reach their final plateau and they may be treated beyond 3 years • **Non-responders**: if no meaningful VA improvement is demonstrated within the first 2 years treatment should be discontinued. Based on recent evidence and expert consensus, the recommended treatment guidelines are made, where; • All patients with a confirmed diagnosis of LHON to be offered treatment with idebenone. • Clinical benefit will be assessed by appropriate experts primarily using VA relative to the 'nadir' (the worst recorded VA). • A responder would be defined as someone who's had a meaningful VA improvement from nadir. Once their new plateau has been confirmed by repeated measures, treatment can be stopped. • If a patient has failed to show a response by 2 years treatment should be stopped. Given these treatment guidelines developed through conversations between the company and clinical experts during ACD2, the company maintains that using the time to indication to treatment discontinuation KM estimates is an accurate and clinically appropriate approach for modelling the duration of treatment and will reflect current clinical practice. This approach is informed by insights gained from the RHODOS, EAP and LEROS studies and aligns with clinical experts' understanding of idebenone treatment. As previously stated, the time to indication to treatment discontinuation curve is formed using the following criteria: • Patients who experience a CRR from baseline within 2 years and are then treated for additional 6 months without further CRR, • Patients who have no CRR from baseline within 2 years, with a CRR defined as an improvement of at least 2 lines in best BCVA or a change from off-chart to on-chart results by at least 5 letters. In clinical trials, a CRR is defined as a response of 10 letters (2 lines) or more for on chart improvement or off-chart to on chart by at least 5 letters. This is a relatively rigid / high bar and has been adopted for the purposes of modelling and cost-effectiveness. However, there is a degree of normal variability in VA assessments, so it is important that treatment decisions are guided by VA change and CRR and made by appropriate experts in consultation with patients. **Treatment duration**

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	At the ACM2, "*the clinical patient and patient experts broadly agreed that the company's proposal of how idebenone would be stopped reflected clinical practice*". However, the committee noted that "*clinical and patient experts agreed that, in clinical practice, there would be some people who would want to have the treatment beyond 36 months, and for whom this would be appropriate. So, the committee was concerned that idebenone may not be used in line with the company's proposed stopping rule."* To further validate the definition of the time to treatment curves and gather clinical input on the expected proportion of patients treated beyond 36 months, the company conducted a clinician validation meeting on the 24th of April 2025, during which both curves were presented.[5] Both clinicians strongly agreed that most patients would be off treatment by 36 months with one clinician stating that "[redacted] *was an appropriate proportion of patients who would likely remain on treatment after 36 months, and that she does not expect this percentage to exceed* [redacted]". The clinician further highlighted that the company's time to indication to treatment discontinuation curve *"provided a more coherent and realistic representation of clinical practice"* compared to the time to treatment discontinuation curve adopted by the EAG. The clinician also stated that "*in her experience, she had observed some patients who showed continued improvement in VA up to 24 months, but by 36 months, she had not seen any patients continuing treatment beyond that point*". This observation was consistent with the findings of another clinician who stated that "*most patients would be off treatment by 36 months, with very few patients on treatment more than 36 months and that any patients taking up to or more than 5 years is exceedingly rare and that all patients should be off treatment within 4 to 5 years*".[5] Concerns about the prolonged treatment durations observed in the EAP study were raised by clinicians during the meeting. Both clinicians raised issues with the study's design, emphasising that it was conducted across multiple countries with differing healthcare systems and treatment practiced. They highlighted that this heterogeneity likely introduced variability that may have skewed the data on treatment on duration. One clinician specifically questioned the clinical appropriateness of the extended treatment durations, suggesting they may not reflect clinical practice. These expert insights further underscore the limitations of using the EAP data to interpret time on treatment in the integrated analysis. Both clinicians also strongly disagreed that approximately [redacted] of patients would remain on idebenone at 9 years as estimated by the time on treatment discontinuation curve adopted by the EAG, with one clinician describing the estimate as "*farfetched*".[5] Based on clinicians' input, from two separate clinician validation meetings that most patients would be off idebenone treatment by 36 months, the company would like to emphasise that the EAG's time to discontinuation curve does not accurately represent idebenone treatment duration in clinical practice. For these reasons, the company would like to reaffirm that it is highly unlikely for a large proportion of patients to be on treatment beyond 36 months, such as those seen in the EAG time to treatment discontinuation curve. The company remains confident that the time to indication to treatment discontinuation KM estimates from the integrated analysis is the most appropriate source to inform idebenone treatment duration. These estimates more accurately reflect real-world clinical practice, as validated by clinicians at two separate clinician validation meetings. However, the company acknowledges that as part of ACM2, clinicians noted that they may expect to see a small proportion of patients still on an upward trajectory at 36 months and would therefore prefer to maintain them on treatment. Whilst the company's time to indication to treatment discontinuation curve already assumes that 0.08% of patients remain on treatment after 36 months until 54 months, with which the clinicians have agreed as part of the recent clinical validation meeting (24th April 2025), additional scenarios have been explored to conservatively model a

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	higher number of patients on treatment for longer than 36 months. A scenario analysis was conducted where [redacted] of patients were assumed to continue treatment for an additional two years post-month 36. This assumption aligns with comments from the most recent clinician validation meeting, where one clinician estimated that approximately [redacted] of patients may remain on treatment beyond three years, and both clinicians agreed that no patients would continue treatment beyond five years. Incorporating this assumption resulted in only a minimal impact on the ICER, with the company's base-case ICER increasing from £28,241 to £28,637 (an increase of £396). Based on the feedback from clinicians, the company's proposed stopping rule at ACM2 has now been revised. The treatment duration is no longer governed by a formal stopping rule but is now aligned with the criteria outlined under the "*treatment guidelines formed from company and clinicians*" section. **Maintenance of treatment benefit after treatment discontinuation** As outlined in the Summary of Product Characteristics of idebenone, according to the biochemical mode of action, idebenone is thought to re-activate viable but inactive retinal ganglion cells (RGCs) in LHON patients by restoring cellular energy (ATP) generation. Depending on the time since symptom onset and the proportion of retinal RGCs already affected, idebenone can promote recovery of vision in patients who experience vision loss.[8] Once patients have stabilised and treatment has been discontinued, there is no indication of a waning treatment effect. As previously discussed in clarification questions (November 2023) question B7, best VA at the RHODOS-OFU (n=58) visit improved in the idebenone group (n=39) with a mean change in logMAR -0.134, corresponding to an improvement of six letters.[9] 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 (n=85) to RHODOS-OFU (n=58) favouring idebenone.[9] 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).[9] The difference between idebenone and placebo remained stable, confirming the sustained treatment benefit of idebenone 24 weeks after the end of a six-month treatment course, and extending beyond 2.5 years without further treatment. The clinical data indicate that patients may continue to improve even after stopping idebenone, suggesting that if treatment is discontinued while patients are still on an upward trajectory, they may continue to experience clinical benefits. To date, there have been no reported instances in clinical practice of patients requiring retreatment following discontinuation, reinforcing the sustained efficacy of idebenone treatment and indicating no evidence of waning treatment effect. Based on this evidence, it is very unlikely that patients would remain on treatment longer than necessary once stabilisation is achieved. Clinicians have stated that, in practice, idebenone would typically be used for up to 2 years if a patient is responding, or until stabilisation occurs. This aligns with the data from the RHODOS-OFU study, which suggest that patients may still continue to improve even after discontinuing idebenone treatment. Furthermore, evidence from natural history studies and the RHODOS trial indicates that cell death does not continue indefinitely in LHON, implying that long-term treatment may not be necessary in most cases. The company are aware that the EAG have requested a scenario in which the time to indication to treatment discontinuation KM curve is reflected in clinical efficacy. Based on the evidence provided above, once the stabilisation in VA is achieved, it will be maintained and will not deteriorate, even if the treatment with idebenone is stopped. Therefore, the clinical effectiveness observed in the clinical studies and included in the transitions probabilities from the integrated analysis will be achieved and maintained even with a shorter duration of treatment captured in the time to indication to treatment discontinuation curve. Therefore, no further scenarios were explored.

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	In conclusion, the company remains confident that the company's time to indication to treatment curve is the most appropriate source for estimating treatment duration in patients receiving idebenone. This approach has been validated by clinicians, with data showing that only a small proportion of patients (approximate [redacted]) remain on treatment beyond 36 months up to 54 months. Clinicians have strongly disagreed with the time to treatment curve adopted by the EAG, which assumes that approximately [redacted] of patients continue treatment at 9 years. The company, however, aligns with clinicians in acknowledging that a small proportion of patients may remain on treatment at 36 months and have explored additional scenario which results in minimal impact on the ICER. The revised company base-case is presented in Table 9.
3. Caregiver HRQoL	**The company strongly considers it appropriate to include a caregiver disutility in the base-case CEA to accurately capture the burden of LHON and the value of idebenone. The impact of caring for a patient with LHON imposes a substantial QoL burden to caregivers, as evidenced in the literature.** The company base-case at ACM2 included caregiver disutility for patients with a LogMAR of 1.0 and higher and these values were derived from a study by Wittenberg *et al.* (2013), as aligned with HST 11.[10,11] The EAG recognises that "*patients experiencing blindness will require additional assistance from a caregiver*", however, the EAG preferred a base-case without caregiver disutilities and instead explored the impact of including caregiver disutility as a scenario. The company does not think it is reasonable to exclude caregiver disutility in the base-case, as LHON affects the QoL of caregivers, impacting their lives, emotional well-being and employment.[12] At the clarification stage, the EAG asked the company to remove the caregiver disutility from patients who would be in residential care and "*This had a small impact in the ICER*" (CQ B11). As stated in the DG from ACM2 "*The clinical and patient experts explained that most people with LHON need constant support from family members and carers.*" During expert consultations, clinicians also very strongly stated that caregiver HRQoL should be included within the analysis with one clinician strongly disagreeing with the exclusion and called it "*very critical and harsh to exclude caregiver disutilities*".[7] **<u>The impact on caregiver QoL as demonstrated in literature</u>** The company presented additional evidence in the DG from ACM2 with a study from Ahmadu et al. (2024) which found clear association between caregiver QoL and the burden of caring for adults with severe visual impairment. The study reported: • 86% of respondents reported an impact on their QoL • Increased severity of visual impairment is linked to higher caregiver anxiety, spousal strain, and more intense informal care • High prevalence of depressive symptoms and overcontrolled coping among caregivers, with female caregivers being the most at risk This review shows that caregivers for adults with severe visual impairment have negatively impacted QoL. To further support the growing evidence on the essential role of caregivers for individuals with visual impairment, the updated findings by Ahmadu et al.(2025) included a survey carried out by the LHON Society to capture qualitative and quantitative impacts of living with LHON on people with LHON and their carers.[13,14] In this study, participants reported relying on an average of 1.58 carers, on average of 24.8 days out of 31 per month, reflecting a consistent need for assistance 83% of the time. This translates to an average of 1.30 of continuous support and this finding was consistent

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	across adults and children.[13] This highlights the critical role caregivers play in patients' daily functioning and the impact it has on caregivers' quality of life. The applied disutility of 0.04 in the model is consistent with the findings in the Pennington et al. (2025) study which states that "*We found consistent evidence for the family effect: improving care recipient's HRQoL by 0.1 would improve carer's HRQoL by approximately 0.012. We also consistently found evidence of a small but statistically significant decrement to carer's HRQoL for each additional year of caring. These findings were robust to scenario analyses*".[15] In the model, health states with logMAR values between 0.3 and 1.0 correspond to HRQoL scores ranging from 0.511 to 0.435 (based on HUI-3 values), with a caregiver disutility of 0.04—approximately aligning with the 1:10 ratio reported by Pennington et al. (2025). The health states with logMAR>1 also correspond to HRQoL values starting at approximately 0.357 (HUI-3 values), reflecting the proportional impact of patient HRQoL changes on caregiver well-being, aligning to Pennington et al. (2025). The company would like to reaffirm that the disutility of 0.04 is already a highly conservative assumption, representing only half of what was reported in the Wittenberg et al. 2013 study and disutility is applied only to logMAR>1 where patients are considered legally blind.[11] The company would also like to highlight that, as part of the response to the EAG's clarification questions to the ACD1 response, multiple scenarios were explored assuming caregiver disutility may reduce over time. Scenarios included applying the caregiver disutility of 0.04 for a limited amount of time to 5 to 10 years, followed by a disutility decrement of 0.02 for the remainder of the time horizon, with the ICERs increasing from £28,451 (base-case) to £29,429 and £29,216 respectively.[2] In response to the NICE committee's suggestion in the DGC to consider scenarios including a carer disutility for adults with LHON supported by quantitative evidence, the company conducted an analysis incorporating assumptions from the findings of Ahmadu et al. (2025), which estimated that each LHON patient requires support from approximately 1.3 carers.[13] Given the notable impact of caregiver burden, and the supportive evidence from the Ahmadu et al. (2025) findings, the company considered it appropriate to include the number of carers per patient in the base-case analysis. This approach is consistent with the committee's recommendation to account for the impact on carers' quality of life and to explicitly quantify the number of carers per patient. Incorporating 1.3 carers into the base case results in an ICER of £28,241. A scenario analysis assuming 1 carer increased the ICER to £28,928. LHON is a profoundly debilitating condition, marked by rapid vision loss with over 50% of eyes deteriorating to LogMAR above 1.0 within one week of disease onset. LHON typically manifests in the second or third decade of life, disrupting key milestones such as career development and starting a family. Caregiver support is therefore critical, especially in the early stages as patients adjust to sudden and life-altering vision loss. Therefore, the company remains confident that including caregiver disutility for patients with LogMAR 1.0 or more (not in residential care) in the base-case is reflective of the burden associated with caregiver HRQoL. This approach is supported by clinicians, patient associations and published literature. The inclusion of 1.3 carers per patient, based on the study by Ahmadu et al.(2025), further supports the importance of caregiver involvement in caring for LHON patients. The revised company base-case incorporating 1.3 carers per patient is presented in Table 9.

Key Changes to the company base-case from ACM1

The company has revised the base-case to support appropriate and timely decision-making. The changes to the company base-case are detailed in Table 9.

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Table 9: Revised company base-case, with reference to base-case at ACM2

Economic input	Company's base-case at ACM2	Change(s) made in response to DGC2
Changes in response to key issues		
Integrated analysis	As part of the company's response to NICE's first draft guidance, an integrated analysis dataset was created, incorporating all available clinical data (RHODOS, RHODOS-OFU, EAP, CaRS-I, CaRS-II, LEROS and PAROS) for both idebenone and SoC. To ensure comparability between the idebenone and SoC treatment arms, the company conducted a PSWA using the integrated analysis dataset. Given the availability of RHODOS data, a double-blind placebo controlled RCT, from baseline to 6 months, transition probabilities were derived solely from RHODOS for this period. The PSWA was then used to derive transition probabilities from month 6 onwards.	To address the concerns of the EAG and committee regarding excluding RHODOS from the integrated analysis, the company have re-run the PSWA using the integrated analysis from baseline, now incorporating RHODOS into this weighted analysis. One weight was calculated for the full ITT population of the integrated analysis, from baseline through to month 48.
Time on treatment	The modelling of treatment duration within the CEA was informed using the time to indication to treatment discontinuation KM estimates based on the integrated analysis set.	The time on treatment will still be modelled using the time to treatment indication KM estimates based on the integrated analysis set.
Caregiver HRQoL	The company base-case at ACM2 included caregiver disutility for patients with a LogMAR of 1.0 and higher and caregiver disutility of 0.04 applied across the lifetime horizon of the model.	The company base-case includes caregiver disutility for patients with a LogMAR of 1.0 and higher and caregiver disutility of 0.04 and 1.3 carers per patient applied across the lifetime horizon of the model.
Cost and resource use	At ACM2 the company base case included the following cost and resource use assumptions: 1. Resource use based on a midpoint patient proportion of KOL survey and Meads *et al.* (2003) estimates 2. Applying a £0 blind registration cost 3. Outpatient care costs applied as a one-off cost 4. Supportive living costs applied across the lifetime time horizon 5. Depression costs applied in each cycle in the first 2-years	To address the concerns from the EAG regarding the cost and resource assumptions the company have accepted all the EAG scenarios. The

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Economic input	Company's base-case at ACM2	Change(s) made in response to DGC2
Changes in response to key issues		
		company's updates to the base-case from ACM2 are: 1. Resource use based on Meads et al 2003 (with depression cost for all health states) 2. Applying outpatient care costs for SoC as half of the costs used for idebenone 3. Apply supportive living cost one-off cost 4. Include outpatient care cost to logMAR<1 patients: Yes (set to Meads et al. 2003 values)
Additional changes		
[redacted]	[redacted]	[redacted]

Abbreviations: ACM2 – Second appraisal committee meeting; CEA – Cost-effectiveness analysis; DGC2 – Second draft guidance consultation; EAG – External assessment group; HRQoL – Health related quality of life; ITT – Intent-to-treat; KM – Kaplan-Meier; KOL – Key opinion leader; LogMAR – Logarithm of the minimum angle of resolution; NICE – National Institute for Health and Care Excellence; PAS – Patient access scheme; PSWA – Propensity score weighted analysis; SoC – Standard or care

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Revised company base-case results

Deterministic results for revised base-case

The deterministic cost-effectiveness results for the revised company base-case are presented in Table 10.

Table 10: Revised company base-case ([redacted])

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]	28,241

Abbreviations: ICER - incremental cost-effectiveness ratio; LYG - life years gained; PAS - patient access scheme; QALYs - quality-adjusted life years; SoC – standard of care

Sensitivity analyses for the revised base-case results

The mean PSA results for the revised company base-case, are presented in Table 11. The incremental cost-effectiveness plane is provided in Figure 9 and Figure 10 presents the cost-effectiveness acceptability curve for idebenone versus SoC.

Table 11: Probabilistic analysis results ([redacted])

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Idebenone	[redacted]	[redacted]	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	28,339

Abbreviations: ICER - incremental cost-effectiveness ratio; LYG - life years gained; PAS - patient access scheme; QALYs - quality-adjusted life years; SoC – standard of care

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Figure 9: Cost-effectiveness plane (revised company base-case, [redacted])

Abbreviations: CEP - cost-effectiveness plane; PAS - patient access scheme; PSA - probabilistic sensitivity analysis; QALYs - quality-adjusted life years; SoC – standard of care

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Figure 10: Cost-effective acceptability curve (revised company base-case, [redacted])

*20% variation applied in the PSA, in the absence of SE or CIs.
Abbreviations: PAS - patient access scheme; QALY - quality-adjusted life years; SoC – standard of care

Results of the one-way sensitivity analysis (OWSA) for the top 10 parameters that had the largest impact on the ICER, for the revised company base-case ([redacted]) are presented in Table 12 and Figure 11.

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Table 12: OWSA results (revised company base-case, [redacted])

Parameter	ICER at lower bound	ICER at upper bound
Patient utility - logMAR <0.3	[redacted]	[redacted]
Patient utility - logMAR 1.3-1.7	[redacted]	[redacted]
Patient utility - logMAR 0.3-0.6	[redacted]	[redacted]
Residential care cost (£)	[redacted]	[redacted]
Patient utility - CF	[redacted]	[redacted]
Proportion of patients - Community care - residential care - logMAR 1.3-1.7	[redacted]	[redacted]
Patient utility - logMAR 1.0-1.3	[redacted]	[redacted]
Patient utility - logMAR 0.6-1.0	[redacted]	[redacted]
Proportion of patients - Community care - residential care - CF	[redacted]	[redacted]
Patient utility - LP	[redacted]	[redacted]

Abbreviations: ICER - incremental cost-effectiveness ratio; PAS - patient access scheme; SoC – standard of care

Figure 11: OWSA tornado diagram (revised company base-case, [redacted])

[redacted]

Abbreviations: ICER - incremental cost-effectiveness ratio; PAS - patient access scheme; SoC – standard of care

Table 13: Scenario analysis (revised company base-case, [redacted]) – Company's original 8 health state structure

Parameter	Scenario number	Base-case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
Base-case				[redacted]	[redacted]	**28,241**
Clinical inputs - Integrated data	#1	Logistic model, MNAR (in both treatment arms)	Logistic model, MAR (in both treatment arms)	[redacted]	[redacted]	33,768
Half cycle correction	#2	Included	Excluded	[redacted]	[redacted]	28,136

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Parameter	Scenario number	Base-case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
Number of carers	#3	Inclusion of 1.3 carers	Inclusion of 1 carer	[redacted]	[redacted]	28,928
Time on treatment	#4	Informed using the time to indication to treatment discontinuation KM estimates based on the integrated analysis set.	KM data from the time to indication to treatment discontinuation + 2% of patients on treatment for another 2 years	[redacted]	[redacted]	28,637
	#5		KM data from the time to indication to treatment discontinuation + 1% of patients on treatment for another 2 years	[redacted]	[redacted]	28,352

Abbreviations: ICER - Incremental cost-effectiveness ratio; MAR – Missing at random; MNAR – Missing not at random; PAS - Patient access scheme; QALY- Quality-adjusted life years;

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References

1. NICE. Draft guidance consultation– ID547 Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547]. 2024.

2. NICE. Single Technology Appraisal. Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547]. Committee Papers 2. [Internet]. 2025. Available from: https://www.nice.org.uk/guidance/gid-ta11288/documents/committee-papers-2

3. Chiesi Farmaceutici S.p.A. Data on file: Integrated Statistical Analysis Report. 2024.

4. Chiesi Farmaceutici S.p.A. Data on file: Integrated Statistical Analysis Plan. 2024.

5. Chiesi Farmaceutici S.p.A. Appendix C. Clinician Validation Report. (24th April 2025). 2025.

6. NICE. NICE real-world evidence framework. 2022 Jun; Available from: https://www.nice.org.uk/corporate/ecd9/resources/nice-realworld-evidence-framework-pdf-1124020816837

7. Chiesi Farmaceutici S.p.A. Appendix D. Clinician Validation Report. (17th October 2024). 2024.

8. Electronic Medicines Compendium (EMC). Raxone 150 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) [Internet]. 2022 [cited 2023 May 26]. Available from: https://www.medicines.org.uk/emc/product/2269/smpc

9. NICE. Single Technology Appraisal Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547] Committee Papers [Internet]. 2024. Available from: https://www.nice.org.uk/guidance/gid-ta11288/documents/committee-papers

10. NICE. Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations. HST 11. NICE;

11. Wittenberg E, Prosser LA. Disutility of Illness for Caregivers and Families: A Systematic Review of the Literature. PharmacoEconomics. 2013 Jun;31(6):489–500.

12. Combal JP, Chipot A, Holzinger E, Hillgenberg M, Roche M, Sargent A, et al. Leber Hereditary Optic Neuropathy (LHON): a qualitative study on the experiences and hopes of patients and caregivers. [Internet]. 2017. Available from: http://grouph.com/wp-content/uploads/2017/04/LHON-patient-research-ARVO-2015_leaflet.pdf

13. Ahmadu C, Roberts G, Mumford J, Mumford A. Date on file: Association between caregiver quality of life and the care provided to adults with severe visual impairment: A systematic literature review. Initiate Consultancy; 2025.

14. LHON Society. LHON Society Response to consultation. Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547]. 2025.

15. Pennington BM. Unpaid Caring and Health-Related Quality of Life: Longitudinal Analysis of Understanding Society (the UK Household Longitudinal Survey). Value in Health. 28(1):138–47.

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Appendix A: Propensity score information

Table 14 presents the propensity score information from the updated weighted analysis carried out from baseline to month 48 in the integrated analysis.

Table 14: Propensity Score Information

Observations	Idebenone						SoC						Treated-control
	N	Weight	Mean	SD	Min	Max	N	Weight	Mean	SD	Min	Max	Mean difference
All	409		0.5611	0.1796	0.1534	0.9701	437		0.4107	0.1779	0.1442	0.8934	0.150
Region	402		0.5544	0.1737	0.1534	0.8925	437		0.4107	0.1779	0.1442	0.8934	0.144
Weighted	402	405.18	0.4797	0.1896	0.1534	0.8925	437	436.38	0.4827	0.1932	0.1442	0.8934	-0.003

Abbreviations: Min – minimum; Max – maximum; SD – standard deviation; SoC – standard of care

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 23 May 2025. Please submit via NICE Docs.

Appendix B: Propensity score weight by visit

Table 15 and Table 16 presents the weighted characteristics at month 6 and month 12, respectively.

Table 15: Patient characteristics at month 6 from the integrated analysis, weighted (Idebenone, N=374; SoC, N=260)

Parameter		Idebenone	SoC
Gender	Male, (%)	[redacted]	[redacted]
	Female, (%)		
Mutation	G11778A		
	G3460A		
	T14484C		
	Other		
Laterality	Bilateral		
	Unilateral		
Analysis age (at first onset), mean (SD)			
Time from first onset at baseline (months), mean (SD)			
Baseline best visual improvement (LogMar), mean (SD)			

Abbreviations: LogMAR – Logarithm of the minimum angle of resolution; SD – Standard deviation; SoC – standard of care

Table 16: Patient characteristics at month 12 from the integrated analysis, weighted (Idebenone, N=285; SoC, N=113)

Parameter		Idebenone	SoC
Gender	Male, (%)	[redacted]	[redacted]
	Female, (%)		
Mutation	G11778A		
	G3460A		
	T14484C		
	Other		
Laterality	Bilateral		
	Unilateral		
Analysis age (at first onset), mean			
Time from first on set at baseline (months), mean			
Baseline best visual improvement (LogMar), mean (SD)			

Abbreviations: LogMAR – Logarithm of the minimum angle of resolution; SD – Standard deviation; SoC – standard of care

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 23 May 2025. Please submit via NICE Docs.

Appendix C: Clinical validation report (24th April 2025)
Please find Appendix C attached as a separate document to this response.

Please return to: **NICE DOCS**

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 23 May 2025. Please submit via NICE Docs.

Appendix D: Patient numbers per treatment arm at each timepoint in the integrated analysis

Table 17: Number of missing and included patients in the integrated analysis

	Baseline	Month 6	Month 12	Month18	Month 24	Month 30	Month 36	Month 42	Month 48
Number of patients included									
Idebenone	402	374	285	243	205	58	53	30	37
SoC	437	260	113	59	55	33	33	32	116
Number of missing patients									
Idebenone	0	28	117	159	197	344	349	372	365
SoC	0	177	324	378	382	404	404	405	321

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 23 May 2025. Please submit via NICE Docs.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. 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 submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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.

Please return to: **NICE DOCS**

Appendix C: Clinical validation (24th April 2025)

C1.1 Introduction and objectives

Introduction

Opinion from two clinicians of Leber's hereditary optic neuropathy (LHON) in England and Wales were sought to support the response to an appraisal consultation document, following the second draft recommendation by the National Institute for Health and Care Excellence (NICE) to not recommend idebenone for LHON.

The following uncertainties were identified by the committee and the External Assessment Group (EAG) in the base case proposed by the company:

- Excluding data from the integrated analysis from baseline to month 6 when deriving transition probabilities and applied data from the RHODOS study only,
- Using baseline distribution of patients from the integrated analysis instead of RHODOS but using transition probabilities from RHODOS for the first 6 months,
- Using time to indication to treatment discontinuation Kaplan-Meier estimates instead of time to treatment discontinuation

In response to the second draft guidance, the company explored additional analyses to address the uncertainties raised by the committee, including an updated weighted analysis evaluating the clinical effectiveness of idebenone versus SoC from baseline, including the RHODOS data. The company aimed to validate this updated weighted analysis with clinicians during the validation meetings as detailed in this report.

Both clinicians have experience treating LHON in England and Wales, are familiar with LHON supportive care, and have an appropriate clinical background. Additionally, both clinicians served as key clinicians for two appraisal committee meeting (ACM) meetings conducted on the 3rd of April 2024 and the 11th of February 2025.

Aims and Objectives

Two interviews were performed, one with each clinician. The overall aims and objectives of the clinician interviews were to:

- Share the outputs of the analysis,
- Obtain validation on whether the analysis and assumptions are in line with expectations in clinical practice,
- Discuss the expected duration of idebenone treatment and the proportion of patients that would be on treatment beyond 3 years.

C1.2 Participants and interview formatting key

Participants

Clinicians were selected based on knowledge of LHON and experience with idebenone usage from clinical trials or compassionate use schemes and recruited for the interviews.

The details of each expert participant are detailed below:

- Professor Patrick Yu Wai Man – Professor of ophthalmology at University of Cambridge, Consultant neuro-ophthalmologist at Addenbrookes Hospital, Cambridge and Moorfields Eye Hospital, London.
- Professor Marcela Votruba – Professor of Ophthalmology at Cardiff University School of Optometry and Vision Sciences and an Honorary Consultant Ophthalmologist at the University Hospital of Wales, Cardiff.

The interviews for each clinician were conducted separately on a teleconference over Microsoft Teams on 24th April 2025.

Interview formatting key

The formatting key for the interview and responses is captured in Table 1.

Table 1: Formatting key

Item	**Format**
Full interview questions	Black text
Participant responses	Red text

	PY: Professor Patrick Yu Wai Man MV: Professor Marcela Votruba

C1.3 Pre-read materials

No pre-read materials were provided prior to the interview. The slide deck was prepared in PowerPoint and presented on the day of the interview. The slide deck can be found in Appendix 1: Clinical validation interview slide deck.

C1.4 Discussion guide and consolidated responses

The discussion guide can be found below. Insights from the clinicians are presented in red font throughout the discussion guide directly under each question. A qualitative analytic approach was used to collate the responses to each question.

Discussion guide

Interview process: Each clinician was interviewed separately. The interviews were conducted by a member of the FIECON team with additional support from the Company over Microsoft Teams. The interviews lasted for approximately 45 minutes each. All respondents were asked open- and close-ended questions, asked to provide rationale and explanation for all answers, and probed further where required.

Other guidance: Questions were presented on the relevant slides to help guide the discussion. Probing questions were used as "follow-up" questions in the absence of clarity in responses.

FIECON interview team: All team members conducting interviews have completed the British Healthcare Business Intelligence Association training for Legal and Ethical Guidelines for Healthcare Market Research and Adverse Event Reporting in Market Research.

Adverse Event reporting: FIECON are required to pass on to the client details of adverse events/product complaints pertaining to their products that are mentioned during the interview. If this happens, the interviewer will need to collect details and report the event, even if the clinician has already done so via the Medicines and Healthcare products Regulatory Agency (MHRA's) 'Yellow Card' system. The

clinician would be asked whether they consent to us passing their details to the client company’s drug safety department for their follow-up.

Introduction and objectives

The following content was presented visually on slides and verbally narrated during the discussion, summarised here for reference:

"Thank you for agreeing to participate in this interview today. The discussion will last about 45 minutes.

Our discussion today will be about the treatment of Leber's hereditary optic neuropathy (LHON) in England. Following a negative draft recommendation from NICE after the second committee meeting for the appraisal of idebenone on February 11th 2025, the Company is preparing to submit a response on May 23rd 2025. In line with the recommendations by NICE and the EAG, the company has explored additional analyses to address the uncertainties raised, including updating the weighted integrated analysis to assess the clinical effectiveness of idebenone vs SoC from baseline, including the RHODOS RCT data.

The objective of this conversation is to obtain UK-specific validation and clinical insights into the outputs of the analysis, to discuss with you the expected duration of idebenone treatment and the proportion of patients that would be on treatment beyond 3 years and to support the response to the appraisal documentation."

Both participants agreed for the interview to be recorded.

Integrated analysis

First, we will discuss on the additional analyses conducted and the updates of the weighted analysis and how this analysis captures the trajectory of idebenone's outcomes, as detailed in slides 13 to 16.

Q1. In the RHODOS only baseline distribution, [redacted] of patients have logMAR>1 but in the integrated analysis (including RHODOS) baseline distribution [redacted] of patients are logMAR>1. Is it reasonable to assume that [redacted] of patients will be starting in logMAR>1 in clinical practice once idebenone is readily available and the process of diagnosing patients with LHON is expected to improve? (slide 13 - *The company has applied the baseline distribution of patients at baseline from the integrated analysis in the economic model*)

MV commented that the integrated analysis baseline distribution of [redacted] seemed slightly lower than what she would expect, as most patients seen in practice are generally slightly worse off. However, MV acknowledged that the spread of visual acuity for the integrated analysis would be much wider compared to the RHODOS trial, due to variability and heterogeneity of studies included in the integrated analysis. MV agreed that with time, as awareness of LHON improves, she would expect to start patients on treatment earlier, with better vision.

PY noted that the RHODOS trial was skewed towards more chronic patients compared to other studies. PY stated that he would expect to see patients much sooner and anticipate a lower percentage of patients with worse logMAR values compared to the one presented for the RHODOS trial.

Q2. As the company has now incorporated the integrated analysis (including RHODOS) data from baseline to measure the clinical effectiveness of idebenone vs SoC across the entire time horizon of the model, do you think it is also appropriate to use the integrated analysis baseline distribution from baseline too? (slide 13 - *The company has applied the baseline distribution of patients at baseline from the integrated analysis in the economic model*)

MV agreed that it seemed reasonable to use the integrated analysis baseline distribution from baseline.

PY agreed that using the integrated analysis baseline distribution from baseline was appropriate, as it provided a more realistic representation of clinical practice.

Q3. The proportion of patients with each mutation appears similar across RHODOS RCT compared to the weighted integrated analysis (including RHODOS). Do you agree that the updated integrated analysis data on mutation types best reflect what is observed in clinical practice? (slide 14 - *The proportion of patients across each mutation in the integrated analysis is similar to those in RHODOS RCT only*)

MV commented that the mutation G3460A seemed quite high in comparison to her experience in clinical practice, while the T14484C percentage looked reasonable. She noted that she would have expected the G11778A mutation to be slightly higher, likely ranging from [redacted]. MV also observed that the percentages of

different mutations between the RHODOS RCT and integrated analysis did not differ significantly.

PY found it reassuring that the proportions of each mutation were similar across both the RHODOS RCT and integrated analysis. He agreed that the data were representative of what is typically seen in clinical practice, specifically noting that the proportion of G11778A mutations was approximately [redacted].

Q4. Are the outputs from the company's economic model reflective of what you would see in clinical practice for the change in logMAR from baseline at each timepoint? (slide 15 – *The trend from the economic model outputs demonstrates that idebenone has a favourable treatment effect compared to SoC – based on the company's updated weighted analysis*)

MV noted that the figures in the table were not significantly different from one another but also found it challenging to interpret the table.

PY stated that the results made sense in terms of improvement from baseline vision but commented that the table was difficult to understand.

Q5. The difference demonstrated at month 6 are driven by a half-cycle correction applied in the economic model, do you consider the difference of logMAR [redacted] between the outcome of the model and the outcome of the integrated analysis to be clinically significant? (slide 15 – *The trend from the economic model outputs demonstrates that idebenone has a favourable treatment effect compared to SoC – based on the company's updated weighted analysis*)

MV considered a difference of logMAR [redacted] (approximately [redacted] at month 6 to be neither significant nor meaningful. She noted that, at this stage, patients may still be stabilizing, making it too early to attribute any observed improvement to a therapeutic effect. MV also highlighted that the data at month 6 may be influenced by several factors, such as the timing of onset and the time elapsed since diagnosis. She suggested that the skewing of the data may become less skewed over time, resulting in more consistent findings.

PY did not consider the logMAR [redacted] difference (approximately [redacted] at month 6 to be significantly different.

Q6. Are the outputs from the company's economic model reflective of what you would see in clinical practice for the change in logMAR from baseline at each timepoint? (slide 16 – *The trend from the economic model outputs demonstrates that idebenone has a favourable treatment effect compared to SoC – based on the company's updated weighted analysis*)

MV noted that the SoC patients are not a uniform group, making it challenging to make generalisations about them in this table, which encompasses all mutations. While she did not dismiss the relevance of the data to clinical practice, she expressed uncertainty about how to validate its accuracy.

PY observed that the data were generally similar across all time points, with the exception being month 6.

Q7. The difference of logMAR [redacted] at month 6 is due to the application of the half-cycle correction (HCC) in the model. The HCC is applied in an economic model to account for the fact that events or transitions between states can occur at any point within a given cycle, not just at the beginning or end. If the HCC is removed from the economic model in the first 3-month cycle, the difference between the model and the integrated analysis at month 6 is less than logMAR [redacted]. Do you consider the difference of logMAR [redacted] between the outcome of the model and the outcome of the integrated analysis to be clinically significant? (slide 16 – *The trend from the economic model outputs demonstrates that idebenone has a favourable treatment effect compared to SoC – based on the company's updated weighted analysis*). *[update: Based on the final economic model, the difference of logMAR at month 6 is* [redacted] *when HCC is applied.]*

MV considered a difference of logMAR [redacted] (approximately [redacted]) at 6 months to be clinically insignificant.

PY noted that a difference of logMAR [redacted] (approximately [redacted]) was reasonably different but still fell below the 10-letter threshold.

Time on treatment

Next, we will discuss on how we model time on treatment in the economic model.

Q8. Is it consistent with clinical practice that a small proportion [redacted] of patients would remain on treatment after month 36? (slide 18 – *At month 36,* [redacted] *of patients are still on treatment using time to indication of treatment discontinuation curve (Company's base case)*)

MV agreed that [redacted] was an appropriate proportion of patients who would likely remain on treatment after 36 months, and she did not expect this percentage to exceed [redacted] In her experience of treating LHON patients with idebenone, she had observed patients who showed continued improvement in visual acuity (VA) up to 24 months. Some patients (i.e. slow responders) may still experience improvement in VA beyond 24 months, but by 36 months, she had not seen any patients continuing treatment beyond that point.

MV also expressed concerns about the long-term treatment duration, questioning whether patients would still be on treatment at 54 months. Chiesi/FIECON clarified that the data beyond 36 months were likely driven by the EAP study. MV noted that the EAP study's rules were not clearly specified and clinicians in the study were from different countries with different healthcare settings and questioned whether prolonged treatments were necessary. MV further highlighted that "*we might see even fewer patients continuing for a longer period of time in the future*".

PY commented that the proportion makes sense and agreed that most patients would be off treatment by 36 months. Furthermore, when discussing the number of patients on treatment post month 36 in Q11 PY agreed with the company's model with [redacted] of patients on treatment and that all patients should be off treatment by approximately 4.5 years.

Q9. Which definition best reflects what you would see in clinical practice (please refer to the figure on the previous slide if needed? (slide 19 – *At month 108, ~20% of patients are still on treatment using time to treatment discontinuation curve (EAG's preferred base case)*)

MV agreed that the previous data (Q8; company's time to indication to treatment discontinuation KM curve) provided a more coherent and realistic representation of clinical practice. In her experience, MV had observed patients who showed continued improvement in visual acuity (VA) up to 24 months, but by 36 months, she had not seen any patients continuing treatment beyond that point.

PY commented that from personal experience, most patients would be off treatment by 36 months, with very few patients on treatment more than 36 months. Any patients taking up to or more than 5 years is "*exceedingly rare*" and that most people should be off treatment within 4 to 5 years.

Q10. Do you think it is appropriate to assume that 20% of patients will still be receiving treatment with idebenone at 9 years, regardless of their response? (slide 19 – *At month 108,* [redacted] *of patients are still on treatment using time to treatment discontinuation curve (EAG's preferred base case)*)

MV strongly disagreed that [redacted] of patients would still be receiving treatment with idebenone at 9 years.

PY disagreed that [redacted] of patients would still be on treatment at 9 years, describing it as "*farfetched*". PY further commented that most patients would be off treatment by 4 to 5 years. Additionally, PY expressed a concern about the EAP study itself, noting that its multinational design may have compromised its evidence-based approach.

Q11. What proportion of patients would you expect to still be on an upward trajectory after 36 months, and for how much longer would you expect to keep them on treatment? (slide 20 – *The company has included functionality to the model to include a proportion of patients who might be on treatment beyond 36 months*)

MV noted that in her clinical practice, she had not observed any patients who were still on an upward trajectory of improvement at 36 months. She further suggested that it was reasonable to expect a few patients to continue improving at this point, but only a small percentage, "[redacted]" would do so for a maximum treatment duration of up to 2 years after 36 months.

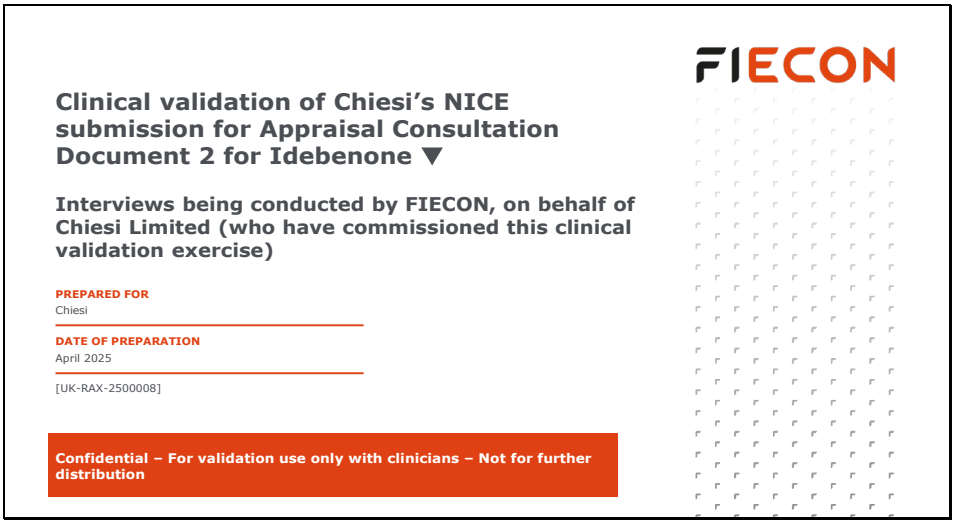
PY acknowledged that while a few patients might remain on treatment beyond 36 months, he agreed with the company's model that all patients should be off treatment by approximately 4.5 years. PY did not provide a definite estimate for the percentage of patients who would still be on treatment after 36 months but has previously agreed with the proportion to Q8 (company's time to indication to treatment discontinuation KM curve).

End of discussion.

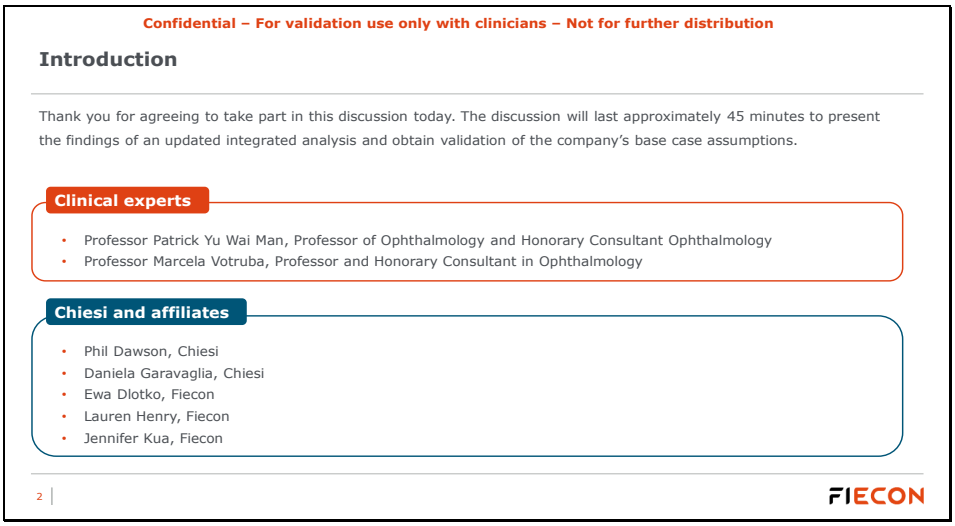
Appendix 1: Clinical validation interview slide deck

The following slides were presented during the interview.

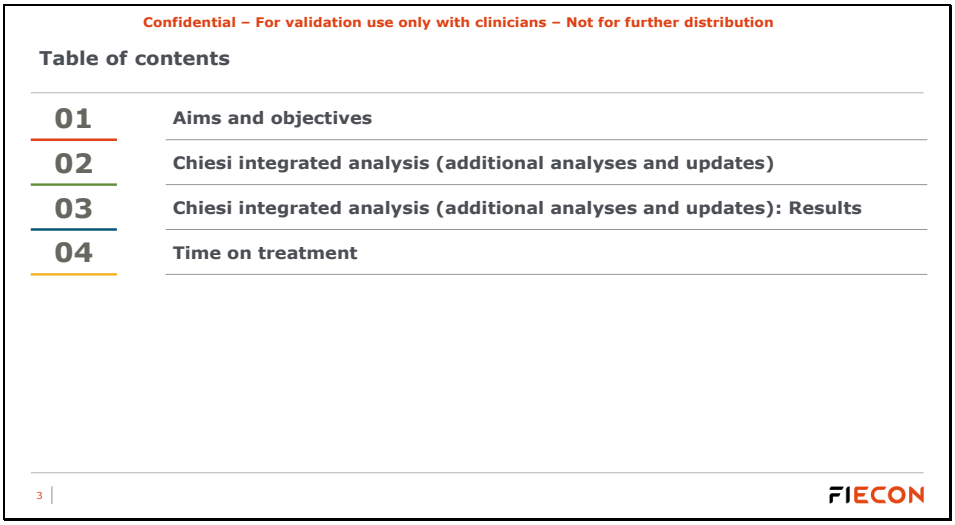
Slide 1



Slide 2



Slide 3



Slide 4

Aims and objectives

Slide 5

Chiesi's progress with idebenone in England

Timeline of authorisation and UK HTA recommendations in UK	
2023	Idebenone was re-considered for guidance development by the Topic Selection Oversight Panel (TSOP) at NICE in January 2023. The panel concluded that idebenone meets the selection and eligibility criteria and has been selected for evaluation. Chiesi submitted the appraisal dossier in October 2023.
2024	The first committee meeting for the appraisal of idebenone occurred on 3rd April 2024, followed by a negative draft recommendation from NICE.
2024	Chiesi submitted a response to the negative draft recommendation on November 15th 2024.
2025	The second ACM occurred on February 11th 2025, followed by a negative draft recommendation from NICE
2025	Chiesi will submit a response to the negative draft recommendation on 23rd May 2025.
2025	The third ACM is set for 8th July. Chiesi aims to gain a positive recommendation for idebenone in the treatment of LHON in Q3 2025

Abbreviations: *ACM – Appraisal committee meeting; HTA – Health technology assessment; LHON – Leber's Hereditary Optic Neuropathy; NICE – National Institute for Health and Care Excellence; TSOP – Topic Selection Oversight Panel; UK – United Kingdom*

FIECON

Slide 6

Chiesi would like to gain expert validation and insights to support the NICE appraisal consultation document response of idebenone for the treatment of patients with LHON

Rationale and background:

- As part of the company's response to NICE's first draft guidance, an integrated analysis dataset has been created, incorporating all available clinical data for both idebenone and SoC. From the integrated analysis dataset, a propensity score weighted analysis (PSWA) was carried out to ensure the clinical effectiveness between the idebenone and SoC treatment arms were comparable.
- Chiesi received draft negative recommendation from NICE, with the following uncertainties identified by the committee in the base case proposed by the company:
  - Excluding RHODOS in the PSWA of the integrated analysis. The company's model included:
    - Transitions probabilities (TPs)* from baseline to 6 months were derived from the RHODOS study (not from the integrated analysis)
    - TPs from month 6 on onwards were derived from the integrated analysis
  - Using baseline distribution of patients from the integrated analysis instead of RHODOS
    - The company baseline population distribution used in the model was based on the integrated analysis ITT baseline distribution which included RHODOS data. The EAG however preferred to use RHODOS only to inform baseline characteristics and distribution in the model as RHODOS was used to model transitions from baseline to month 6.
  - When people would stop treatment with idebenone in clinical practice
    - The committee was concerned that idebenone may not be used in line with the company's proposed stopping rule as there would be some patients who would want to continue treatment beyond 36 months. The committee noted that the efficacy in the model was based on treatment duration in the integrated analysis set and further added that the company had not proposed any adjustments to reflect the impact of shorter treatment duration associated with the stopping rule on the idebenone efficacy. The committee thought that the EAG's approach was more appropriate which applied the time to treatment discontinuation KM from the integrated analysis, allowing patients to remain on treatment for up to 9 years.
  - Lack of quantifiable evidence on carer disutility
    - The committee acknowledged that adults with LHON may need assistance but had not seen any evidence.
- Following the release of the draft guidance, Chiesi has explored additional analyses to address the uncertainties raised by the committee in the draft guidance, including an updated analysis evaluating the clinical effectiveness of idebenone versus SoC from baseline from the integrated analysis.

**Transition probabilities are defined as the likelihood of a patient moving from one health state to another and are applied per model cycle.*
Abbreviations: *ACD – Appraisal consultation document; EAG – External assessment group; ITT – Intention-to-treat; KM – Kaplan Meier; LHON – Leber's hereditary optic neuropathy; NICE – National Institute for Health and Care Excellence; PSWA – Propensity score weighted analysis; TPs – Transition probabilities*

FIECON

Slide 7

Chiesi would like to gain expert validation and insights to support the NICE appraisal consultation document response of idebenone for the treatment of patients with LHON

The aim of the interview is to:

- Share with you the outputs of the analysis and obtain validation that they are in line with expectations of clinical practice.
- Discuss with you the expected duration of idebenone treatment and the proportion of patients that would be on treatment beyond 3 years

The objectives are to:

- Support the response to the appraisal consultation document following the draft recommendation to not recommend idebenone for LHON due to uncertainties in the clinical data.

Abbreviations: *LHON – Leber's hereditary optic neuropathy; NICE – National Institute for Health and Care Excellence*

FIECON

Slide 8

Chiesi integrated analysis (additional analyses and updates)

Slide 9

The company has conducted an integrated analysis (including RHODOS) from baseline to mitigate the concerns highlighted by NICE and the EAG

- Based on the feedback on the original submission from the EAG and NICE, the company developed an **integrated dataset**, using all the data from all the previous studies to support the clinical and economic value of idebenone for **re-submission**.
- To analyse the complete clinical idebenone landscape the integrated analysis set was created using data from the RHODOS-OFU, EAP, CaRS, CaRS II, LEROS, and PAROS studies. Due to the non-linear nature of the data, all the analysis on clinical efficacy have been performed excluding data before 12 Months from baseline. The company model **used baseline distribution from the integrated analysis**. **Transition probabilities** for idebenone and standard of care were derived using:
  - Baseline to month 6: RHODOS RCT data only
  - Month 6 – month 12: Integrated analysis using a PSWA based on stabilised inverse probability of treatment weights
  - Month 12 – month 36: Integrated analysis using a PSWA based on stabilised inverse probability of treatment weights and estimated using a logistic regression model with MAR and MNAR assumptions
  - No transition from month 36 onwards
- The committee and the EAG raised concerns that the company excluded data from the integrated analysis from baseline to month 6 when deriving the transition probabilities and applied data from the RHODOS RCT only.
- Therefore, the company has updated the integrated analysis to assess the clinical effectiveness of idebenone vs SoC from baseline, including the RHODOS data. A new PSWA based on stabilised inverse probability of treatment weights was ran on the total integrated analysis and RHODOS population from baseline through to month 48. This singular dataset was used to derive new transition probabilities from baseline to month 36.

Abbreviations: *CaRS – Case record survey; EAG – External assessment group; EAP – Expanded access programme; ICER – Incremental cost-effectiveness ratio; MAR – Missing and random; MNAR – Missing not at random; NICE – National Institute for Health and Care Excellence; OFU – Observational follow-up; PSWA – Propensity score weighted analysis; RCT – Randomised controlled trial; SoC – Standard of care*

FIECON

Slide 10

Chiesi integrated analysis (additional analyses and updates): Results

Slide 11

Model base case settings

The cost-effectiveness model incorporates the following base case parameters:

Parameters	Definition
Population	Adolescent and adult patients with LHON aged 12 years and older
Intervention	Idebenone
Comparator	SoC consisting of lifestyle management, genetic counselling and supportive treatments
Duration of treatment	Based on the treatment continuation and stabilisation from the integrated analysis
Gender (%)	79% male (baseline characteristics of the ITT population in the integrated analysis)[1]
Discount rate (%)	3.5%*
Time horizon	Lifetime
Perspective	UK NHS and Personal Social Services
Outcome measures	Total costs, total QALYs and ICER

*Costs and health outcomes are predicted to occur in the future are usually valued less than present costs, and so it is recommended that they be discounted in analysis. NICE guidelines recommend that they should be discounted at 3.5% per year – Discount Rate [online]. (2016). York: York Health Economics Consortium; 2016. https://yhec.co.uk/glossary/discount-rate/

1. Chiesi. Integrated analysis – statistical analysis plan. 2024. Data on file.

Abbreviations: ICER – Incremental cost-effectiveness ratio; ITT – Intention to treat; LHON – Leber's hereditary optic neuropathy; NHS – National Health Service; QALY – Quality-adjusted life-year; SoC – Standard of care; UK – United Kingdom

FIECON

Slide 12

The company has adopted the following analysis in the updated base case assumptions for their economic model

Cycle	Both treatment arms (Idebenone and SoC)
Base case	
Baseline distribution	Integrated analysis (including RHODOS), weighted
Baseline to month 12	Integrated analysis (including RHODOS), weighted using a PSWA based on stabilised inverse probability of treatment weights
Month 12 to Month 36	Integrated analysis (including RHODOS), weighted using a PSWA based on stabilised inverse probability of treatment weights and estimated using a logistic regression model and multiple imputation for the missing data with MAR ***or*** MNAR assumptions
Month 36 onwards	Assume no further movement from patients

Abbreviations: *SoC – Standard of care*

FIECON

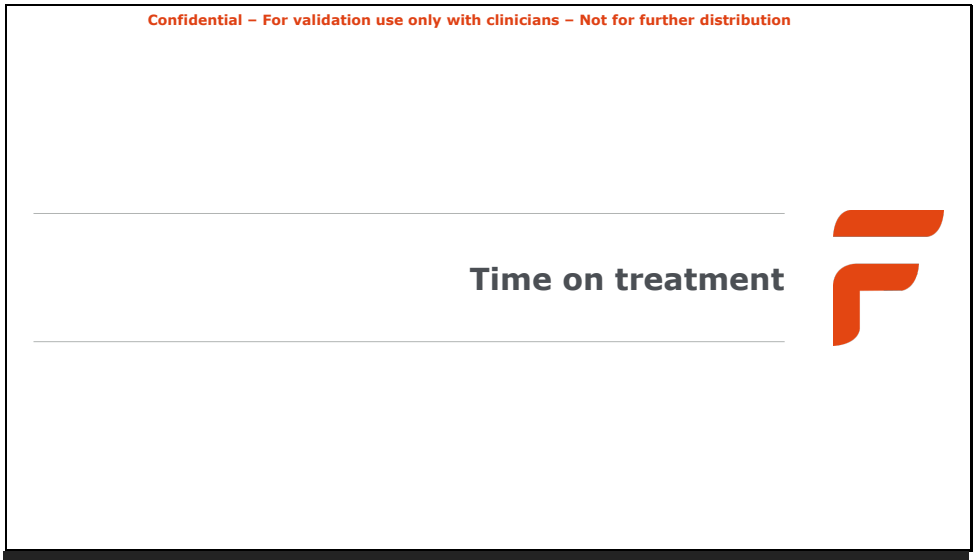
Slide 13

Slide 14

Slide 15

Slide 16

Slide 17



Slide 18

Slide 19

Slide 20

Confidential – For validation use only with clinicians – Not for further distribution

The company has included functionality to the model to include a proportion of patients who might be on treatment beyond 36 months

- At the second ACM, the company assumed time on treatment in accordance with the proposed stopping rule, demonstrated on slide 18. The results into the majority of patients being off treatment by 36 months.
- During the second AMC, both clinical and patient experts agreed that, in clinical practice, if a patient was on an upward trajectory of improvement at 36 months, they would want to continue treatment. Generally, there is a plateau in improvement at 36 months but there will be some people who may still see improvement after 36 months.
- The committee expressed concerns that idebenone may not be used in clinical practice in line with the company's proposed stopping rule.
- The company therefore wish to explore this uncertainty in the economic analysis and wish to run a scenario assuming x% of patients remain on treatment after 36 months for Y years.

Q: What proportion of patients would you expect to still be on an upward trajectory after 36 months, and for how much longer would you expect to keep them on treatment?

Percentage of patients on treatment	Duration of treatment post month 36
e.g. 5%	*e.g. 2 years*

 Abbreviations: *ACM – Appraisal committee meeting; LHON – Leber's hereditary optic neuropathy*

FIECON

Slide 21

LHON Society Response to consultation

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

April 2025

Has all of the relevant evidence been taken into account?	During the process of consultation and committee meetings patient experts and the LHON Society have provided detailed account of the impact of LHON on people living with the condition and their carers. This evidence is relevant and may not have been fully considered. In addition, the LHON Society has carried out a further consultation survey. The full survey findings have been attached and we suggest that comments from patients and carers offer a deeper understanding. The LHON Society carried out a survey of members to capture qualitative and quantitative impacts of living with LHON on people with LHON and their carers. The survey had 38 participants, all of whom consented for use of their responses. Of respondents, 89% were based in England. The survey was conducted in March 2025 through an online survey shared to members of the LHON society. 50% of respondents reported that they have LHON and 50% reported that somebody close to the has LHON. LHON significantly impacts the lives of those affected and their families. It affects independence, emotional well-being, social interactions, and financial stability. Respondents highlighted the daily challenges they face, including the need for constant support, the emotional toll of the condition, and the financial burden of assistive technology and medication. Respondents with LHON require significant support from their close ones for various daily tasks. This support includes guiding, reading, cooking, shopping, personal care, and transportation. Some respondents have learnt to live independently but still need assistance with specific tasks, especially transportation. Carers provide extensive support to individuals with LHON, covering a wide range of tasks. This includes food shopping, computer admin, cleaning, reading mail, financial support, preparing food, crossing roads safely, navigating new settings, household tasks, personal care, and emotional support.

	Carers experience significant emotional, practical, financial, and social impacts while supporting individuals with LHON. The emotional toll includes stress, anxiety, and depression. Practically, carers take on increased responsibilities and face time-consuming tasks. Financially, carers bear the costs of assistive technology, medication, and lost income. Socially, carers may experience isolation and reduced quality of life. This report highlights the significant impact of LHON on both individuals and their carers, emphasizing the emotional, practical, financial, and social challenges they face. When asked the number of carers people had the respondents show an average of 1.58 carers, on average of 24.8 days out of 31 per month (83% of the time). This would reasonably translate to an average of 1.30 carers continually. This finding is consistent across adults and children.
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	The summaries of cost effectiveness do not take into account of the impact of LHON on carers. Qualitative and quantitative evidence of this is provided in the attached survey. We note that the EAGs last estimates of cost effectiveness has altered drastically in the days ahead of presenting to committee, suggesting much uncertainty in their interpretation. We also note comments made in both committee meetings that suggest a lack of understanding of sight loss and LHON.
Are the recommendations sound and a suitable basis for guidance to the NHS?	The LHON society does not agree that the recommendation is a sound or suitable basis for guidance to the NHS. LHON leads to sight loss, which has a profound and lasting affect on the quality of life of both people living with LHON and those caring for them. The appraisal so far seems to disregard many aspects of the affects of sight loss.
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	In the UK, sight loss, when formally identified as either sight impaired or severely sight impaired, automatically qualifies individuals as disabled under the Equality Act 2010. To not fully account for the impacts of sight loss on patients and carers in this appraisal may be considered as discriminating against a group of people. We urge NICE to reconsider its draft guidance and fully take the opportunity to read out survey, listen to patient and clinical experts to improve their understanding of the impact of LHON.

LHON Society Survey:

The LHON Society carried out a survey of members to capture qualitative and quantitative impacts of living with LHON on people with LHON and their carers. The survey 38 participants,

all of whom consented for use of their responses. Of respondents, 89% were based in England. The survey was conducted in March 2025 through an online survey shared to members of the LHON society.

50% of respondents reported that they have LHON and 50% reported that somebody close to them has LHON.

LHON significantly impacts the lives of those affected and their families. It affects independence, emotional well-being, social interactions, and financial stability. Respondents highlighted the daily challenges they face, including the need for constant support, the emotional toll of the condition, and the financial burden of assistive technology and medication.

Respondents with LHON require significant support from their close ones for various daily tasks. This support includes guiding, reading, cooking, shopping, personal care, and transportation. Some respondents have learnt to live independently but still need assistance with specific tasks, especially transportation.

Carers provide extensive support to individuals with LHON, covering a wide range of tasks. This includes food shopping, computer admin, cleaning, reading mail, financial support, preparing food, crossing roads safely, navigating new settings, household tasks, personal care, and emotional support.

Carers experience significant emotional, practical, financial, and social impacts while supporting individuals with LHON. The emotional toll includes stress, anxiety, and depression. Practically, carers take on increased responsibilities and face time-consuming tasks. Financially, carers bear the costs of assistive technology, medication, and lost income. Socially, carers may experience isolation and reduced quality of life.

This report highlights the significant impact of LHON on both individuals and their carers, emphasizing the emotional, practical, financial, and social challenges they face. Below are quotes from the survey that highlight the impacts.

When asked the number of carers people had the respondents show an average of 1.58 carers, on average of 24.8 days out of 31 per month (83% of the time). This would reasonably translate to an average of 1.30 carers continually. This finding is consistent across adults and children.

How does LHON impact your life? Or that of the person who has LHON? For example: Relationships, travel, work, finances

- "My Dad has LHON. The impact that this has had is that over time my Dad has become less independent and relies heavily on myself and the wider family to help with daily tasks."
- "It impacts on everything in my life."
- "LHON does not impact my life, Being Blind does. Being blind impacts every aspect of life. Being blind is the issue, not having LHON. There is not a single aspect of life that being blind does not affect."
- "Literally impacts every aspect of Harvey’s life."

- "Constant worry regarding my nephew. Stress throughout family."
- "It has affected their life enormously going from 2020 vision to virtually blind, they have to be taken everywhere and are unable to do their job anymore."
- "It's been devastating. I feel it's concerning that support is poor and the profile poor. My nephew given diagnosis I was referred by GP and informed I have it. Consultation stressful for me as questions left unanswered. I felt as it's rare I was expecting more support."
- "They need daily help with travelling and getting around safely. Also with day to day tasks such as reading things out and preparing food. They need help whilst shopping for example, reading out dates on food and shopping for clothes."
- "It impacts my life massively, I'm restricted to what I can do in my personal life and for employment. I feel like I'm often a burden to my family and friends and lack self-confidence."
- "Lost my job with the condition and my independence. I can no longer drive, watch the television, and need assistance walking around. I also have to pay for my idebenone, and with no longer working, it has a big financial impact."
- "My daughter has LHON. There has been an impact on her friendships, learning who her friends are/aren't; travel is difficult, which impacts her quest for independence; she has struggled to get PAID work; we support her as parents financially and emotionally."
- "LHON impacts on all aspects of my daily life. I cannot do daily life normal tasks without some level of assistance e.g. shopping, cooking or studying."
- "My mum has it, I'm her daughter (19). For instance, she can cook tea independently but I will have to help her get the correct spices out of the cupboard and check the chicken is cooked etc."
- "Depression, sadness, stress. The inability to see normal things has a massive effect, from simple things like crossing roads, using mobile phones, reading post/bills, helping kids with homework, not being able to read bedtime stories."
- "My severe visual impairment affects every aspect of my life. It is difficult to travel, work and manage my own household management and financial affairs."
- "I am registered visually impaired and went to a 'special school'. I wanted to be a nurse but couldn't due to my vision. I went to work in a care home (the next best thing), so getting ahead in my career took a long time due to the difficulties of not being fully sighted and the stigma of having a sight issue."
- "I have the gene and my brother is blind through LHON. I have a 15-year-old son and it scares me to think that he could go blind and that there is nothing that can be done about it."
- "In every way."
- "My husband is afflicted which means that I am his full-time carer and have to drive him everywhere."

- "I am severely sight impaired, and although I am very determined and have been able to be employed, I am severely restricted in most aspects of my life. I lack independence in most things."
- "In every way. I do work but obviously very limited as to what I am able to do. Depression is always there which inevitably leads to bouts of heavy drinking and the cycle continues."
- "My son developed LHON at the age of 21, being certified blind 3 months later. It was devastating, from being unable to cook, see the food on his plate, not being able to travel, unable to continue with playing and watching sports needing help to find the toilets and unable to use computers or mobiles."
- "My daughter has LHON. She is 14. She needs additional support at home and at school. Whilst she can read large print text up close she cannot read text from a distance or small print like labels or magazines."
- "I can no longer drive, I can't read paper things i.e. letters, bills. I can't read bus destinations, I struggle finding my way when travelling on my own. I can't read labels on food items."
- "LHON has affected my life massively. I was diagnosed with LHON about four years ago, before that I was working as a solicitor and drove a car."
- "My son who is 30 was diagnosed with LHON 2 years ago. He lost his driving licence, his apprenticeship, his confidence and self-esteem."
- "It is very difficult for my daughter to make friends and socialise in unfamiliar environments. She is currently out of education and employment."
- "I started losing my vision in 2021 in my left eye, I was trailed on Idebenone and within 4 weeks it improved my sight."
- "Being legally blind affects every aspect of life. It's how we deal with it that makes the difference between success and failure."
- "Considerably restricts activity of all sorts. Travelling is extremely difficult. Shopping of any kind is impossible."
- "I had to stop working. I cannot cross the street or go outside by myself. I depend on other people for cooking among other house and personal chores."
- "I need to use a magnifying glass to read, shop, cook and magnification on iPad, monitor and at work."
- "LHON affects our lives in every possible way. For example, my husband (who has LHON) used to do all the shopping which involved using public transport."
- "My sister has lost usable sight in both eyes, needs a partner to do the majority of cooking, cleaning, taking them out, etc."
- "My grandson's partial sight has affected his work and travel in that he cannot drive or do certain jobs."
- "It limits life choices and work opportunities."

- "It impacts everything I do. I am often lonely and reliant on others."
- "LHON impacts every part of the person's life. Travel is very difficult. Work is difficult. Relationships and friendships are difficult to initiate."

If you have LHON, do you require support from people close to you? Friends, family, partner? And if yes, how? What tasks do they help with?

- "n/a as I don't have LHON but my Dad requires help with most day to day tasks."
- "Yes for guiding. Help with everyday tasks. I have carers come in to help me to get prepared for the day."
- "I have lived alone for decades and was able to be 100% independent with no assistance from anyone. My mother was a fantastic support to me. It is up to us as to how much support we need and choose. Now that I am married, I welcome the support of my wife mostly for driving me places and help with shopping. I have learnt how to do just about everything with vision loss. We can be independent too."
- "I'm not happy with my referral and appointment at Women's Hospital Liverpool. I felt I should have been tested and I am willing to support any research. I'm still waiting for confirmation if the diagnosis has been documented on my medical records."
- "Provide support travelling, walking around outside of my familiar surroundings. Help with day to day tasks, reading, household duties, safety, finding items, reading instructions for preparing food, washing clothes etc. Assisting me with personal care, i.e. telling me if I have a mark on my clothes etc. Assistance with all forms of shopping. Assistance when out and about, finding toilets, staying safe, road safety."
- "Yes, they help select appropriate clothes to wear, reading out information. Linking arms to walk around. They drive me to places such as the barbers, the dentists and hospital appointments."
- "Support includes every aspect of daily life and limits bigger opportunities."
- "Yes I need support

If you have LHON, do you require support from people close to you? Friends, family, partner? And if yes, how? What tasks do they help with?

- "Provide support travelling, walking around outside of my familiar surroundings. Help with day to day tasks, reading, household duties, safety, finding items, reading instructions for preparing food, washing clothes etc."
- "Yes, they help select appropriate clothes to wear, reading out information. Linking arms to walk around. They drive me to places such as the barbers, the dentists and hospital appointments."
- "Support includes every aspect of daily life and limits bigger opportunities."
- "Yes I need support. I need support with shopping, cooking, reading e.g. a menu in a restaurant and finding my way around places."
- "Help with reading mail and texts, using washing machines, cooking, apps on phones and more."

- "Yes, I need help and support from my family. I need help with shopping, housework, personal finances, cooking and getting around."
- "Yes, my husband, my friends, my colleagues. My husband drives me where I need to go, he hates me travelling on public transport at night, I struggle a lot in the dark."
- "My dad helps my brother with any issues i.e. booking appointments, lifts to places and filling out forms."
- "Yes. I can't live without the help of others."
- "Very much so. I need assistance with getting to places as I live semi-rurally. I need assistance with household management, shopping, finances and basic activities of daily living."
- "Obviously all help is gratefully received in every aspect of life. Travel, cooking, shopping etc."
- "Yes I require support from family with day to day living with banking and food shopping, hard to see prices on clothes and food. Travelling, navigating my way around need help from others."
- "The main tasks are now need help with our driving. I have learnt to do most other things on my own or with the use of a phone with accessible apps etc."
- "My son requires help from his parents and his girlfriend on a daily basis. He needs daily help with getting around, cooking and basic tasks at home."
- "Not anymore as my sight improved with Idebenone."
- "I do not require support as I have learned to live independently. However, support is needed with transport due to not being able to drive."
- "Yes but I manage."
- "Yes, from my spouse and family and we need someone at home to cook and clean and take me out."
- "I live on my own and I am very independent. Luckily I don't need to rely on anyone else yet."
- "My sister needs help with practically everything. Her husband and children support her."
- "Friends and family play an important part in helping me to live a full life."

If you support somebody with LHON, what tasks do you help with?

- "Food shopping, computer admin, cleaning, reading mail."
- "Every day, I help to prepare food by getting ingredients out and reading labels on recipes. Also, I help to cross the road safely and navigate new settings such as walking down stairs safely and finding places."
- "I sort out my son's meals, do his toothbrush. Buy his clothes. Take him out, I try to keep him positive."

- "From waking up to bedtime: preparing food, studying, reading, shopping, setting up support."
- "Both my sons have LHON. My husband drives them around, we help them fill forms in, keep their flats clean, help them financially and mentally, with emotional support."
- "Reading cooking instructions on food. Homework from school - takes the child twice as long and consumes much more of parents' time than other children."
- "Shopping, travel, cooking, eating, cleaning. Everything that he should be able to do for himself."
- "I have supported my daughter in getting access to education, attending meetings/phone calls/emails to smooth the very difficult experience of secondary school with a hidden disability."
- "My mum is fully blind from LHON and needs help with everyday tasks and writing and TV."
- "Cooking, washing, gardening, transport, making travel plans, finance. If we watch TV and there is no audio description I do that. Oh and choosing clothes to wear."
- "I often take my sister swimming or shopping which proves difficult for both of us."
- "Financial assistance."
- "Support for everything."
- "Travel, finances, cooking, cleaning, everything."

What is the impact on those who help people with LHON? Eg financially, emotionally, socially, practically

- "It has a massive impact on my life as the time I spend helping Dad is time taken away from my own family."
- "Emotionally painful to see your loved one no longer able to do basic daily life tasks as they once could and not able to do activities they loved anymore."
- "My husband had depression some time ago, I believe this was the emotional effects of caring for 3 people with LHON. All responsibility for keeping life and soul together falls to him."
- "As a mother, I never knew about LHON. Subsequently, it has been very upsetting. I worry about the future. There is no support, every day I wish for a cure."
- "Financially, emotionally, every way possible it’s such an awful disease."
- "To self-fund medication is obscene. To self-fund appointments to Cambridge obscene."
- "I feel as if I have a greater responsibility than others my age when doing things such as crossing roads when I am responsible for their safety."
- "It is time-consuming. There is a level of constant consideration that the person with LHON is able to maintain a sense of independence, value, and self-worth."

- "My visual impairment has had a major effect on my family members. It has been very distressing for the whole family to discover that a number of us carry the defective gene and could go on to develop LHON."
- "Not only I had to stop working, but my wife has struggled at work because of the amount of additional responsibility. Before the tasks were shared as well as raising the family and working. Now she has to handle all of it, plus support me."
- "Socially, may have to stay closer to her to assist at events. Practically, help with reading labels etc."
- "He always has to drive, pick us up, make sure we're safe and 'be on hand' all the time. It's often stopped him going out himself, having a drink or going to bed early, as he needs to be available for us."
- "My partner is held back by me. I think she is depressed because of looking after me."
- "It changes my life. I have had to take responsibility for the running of the house (e.g., noticing when we have run out of something and packing/unpacking shopping, suitcases, etc.). My husband gets very depressed sometimes and so do I."

Single Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Name	Lily Mumford
Role	Patient expert
Comments on the DG:	

Has all of the relevant evidence been taken into account?

The evidence presented at committee meetings by clinical and patient experts appears to have been ignored in favour of the overly pessimistic view of the EAG, who have repeatedly shown a poor level of understanding of vision loss. During committee meetings clinical and patient experts have given strong representation of LHON and this appears to have been ignored. An example of this is the need for adults with LHON to have carers, failure to understand this after the discussions in committee meetings is very disappointing.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summaries of clinical and cost-effectiveness seem unreasonable considering the very late changes to EAG's preferred cost-effectiveness estimates. As a patient expert, I note that these estimates were reduced considerably from the briefing session to the committee, suggesting potential errors or last-minute changes in the EAG's estimates. I would, therefore, question the reliability of the EAG's estimates.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations do not appear sound and appear to take into account the most pessimistic case of evidence presented and seem to have been changing until the very last moment. The EAG's lack of comprehension has been clear through this process. I would question the fairness and appropriateness of this recommendation and would suggest that a sound recommendation has not been made.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

By denying people in England access to Idebenone, you are potentially taking away the only option people could have to recover or restore some sight. People in other parts of the United Kingdom have access to this treatment. By not allowing access to the only available treatment, you may be discriminating against disabled people.

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

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **11 June 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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.

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	Mary Clifford
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**	My mother first started experiencing problems with her vision 6 years ago and was in hospital undergoing many different tests. Once these test where finished she was then diagnosed with LHON. We as a family were so heartbroken, we all didn't know what LHON was and adjusted to my mums vision loss very quickly. After having genetic testing, me and my 3 brothers have been confirmed of having LHON. I suffer with migraines and whilst having a attack I collapsed and woke up with no vision out of my left eye in September 2022. I then saw my mothers consultant at [redacted] who confirmed that the LHON had manifested in my left eye. This came as a shock as I was told that LHON manifests in women during menopause. During the appointment I was advised by the consultant to trail the Idebenone straight away. Within 3 days I saw a difference in my vision and was told to keep taking this. My consultant had referred me to [redacted] and a ophthalmologist neurologist. He had also requested funding to help pay for the Idebenone as this was being sourced privately which was refused 3 times which felt very demoralising. I then went onto being on my local news to make awareness, started a petition and went to my local MP. By July 2023 my consultant at [redacted] and [redacted] had both said that my visual fields are back to what they were before LHON had manifested and was told to ween off the Idebenone. My 3 consultants have been amazing and I cannot fault the support they have given me and have fought my corner since day 1. My mother on the other hand has been too late with trying Idebenone and hasn't been helped by professionals, i.e the guide dogs have dropped her visual buddy. The hospital have been amazing for her. I have now been off the Idebenone since February 2025. The problem I have had is being told LHON is not a emergency after having a scare and having to wait for my consultant to come back from annual leave, as he is the only consultant who knows

	what LHON is. We need to make more awareness of mitochondrial diseases like LHON.
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?**	A) We have no treatments that I am aware of. I have to buy my Idebenone privately from the US/Poland. I was refused funding 3 times from my local NHS trust. B) It seems very unfair that some NHS trusts help others but others are overlooked as they are not aware of the disease.
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 are no NHS treatments at this time as far as I'm aware.
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**	A) No current NHS treatments for Idebenone if there was in my eyes, taking Idebenone early enough will fulfil quality of life and keep everything positive i.e mental health. B) Idebenone is most important. Without it there could be serious visual impairment. C) There is no disadvantage as this stopped my manifestation and spreading. The disadvantage was when I first started taking the Idebenone and ran out I saw my eye condition deteriorate. But started getting better when I restarted the Idebenone.
10. If there are disadvantages of idebenone over current treatments on the NHS please describe these.	The disadvantage is it is not being prescribed in England. But is in Wales, Scotland and Northern Ireland.

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	I personally think everyone with LHON should be able to have this as a preventor.
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.	This should be available to everyone in England with the condition. No matter what race, disability etc. This should NOT be a postcode lottery or discrimination.
13. Are there any other issues that you would like the committee to consider?	I would like you to consider where you purchase Idebenone from. As you do with other generic products. You can get Idebenone cheaper from in the US and Poland for a fraction of the price that Chesi are suggesting to sell it for.

	The Idebenone I get from the states has been clinically tested as 99.9% the same as the Raxone branded Idebenone.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Idebenone has saved my sight.
- I have carried on being part of the LHON community and carried on working through my treatment (whilst progressing in my career)
- This should not be a postcode lottery.
- You must consider cheaper options not just one brand.
- Make more heightened awareness of mitochondrial diseases within the NHS.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

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]

ACM 3 Clarification questions

[06/2025]

File name	Version	Contains confidential information	Date
ID547 idebenone EAG clarification letter ACM3 to company - company response [Redacted] 6Jun25	**1**	**Yes**	**06/06/2025**

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

A1. Priority question. Please can the company provide density plots for the weights assigned to patients within each trial arm of every study, and the overall SoC and idebenone arms. Furthermore, please provide the total value of the combined weights for the patients within each trial arm of every study. Provide these for the following populations:

(a) All patients;

(b) Only for patients who did not have data imputed (at every time point);

(c) Only for patients who did have data imputed (at every time point).

Due to the limited time allowed to reply to this question, the company decided to provide the information in a tabular format. Summaries have been produced for all the populations and strata requested in terms of frequency of patients, total sum of weights, and percentiles: 5th, 10th, 25th, 50th, 75th, 90th and 95th. Results are contained in the following outputs:

Output	Title	Population
DIST_PSWEIGHTS_ARM	Distribution of PS weights by Arm	Integrated ITT - PS Extended Common Support Region
DIST_PSWEIGHTS_STUDY	Distribution of PS weights by Study	Integrated ITT - PS Extended Common Support Region
DIST_PSWEIGHTS_ARM_STUDY	Distribution of PS weights by Arm and Study	Integrated ITT - PS Extended Common Support Region
DIST_PSWEIGHTS_6M_PRESENT	Distribution of PS weights in patients with data at Analysis Visit Month 6	Integrated ITT - PS Extended Common Support Region
DIST_PSWEIGHTS_6M_MISSING	Distribution of PS weights in patients without data at Analysis Visit Month 6	Integrated ITT - PS Extended Common Support Region
DIST_PSWEIGHTS_12M_PRESENT	Distribution of PS weights in patients with data at Analysis Visit Month 12	Integrated ITT - PS Extended Common Support Region
DIST_PSWEIGHTS_12M_MISSING	Distribution of PS weights in patients without data at Analysis Visit Month 12	Integrated ITT - PS Extended Common Support Region

DIST_PSWEIGHTS_24M_PRESENT	Distribution of PS weights in patients with data at Analysis Visit Month 24	Integrated ITT - PS Extended Common Support Region
DIST_PSWEIGHTS_24M_MISSING	Distribution of PS weights in patients without data at Analysis Visit Month 24	Integrated ITT - PS Extended Common Support Region
DIST_PSWEIGHTS_36M_PRESENT	Distribution of PS weights in patients with data at Analysis Visit Month 36	Integrated ITT - PS Extended Common Support Region
DIST_PSWEIGHTS_36M_MISSING	Distribution of PS weights in patients without data at Analysis Visit Month 36	Integrated ITT - PS Extended Common Support Region
DIST_PSWEIGHTS_48M_PRESENT	Distribution of PS weights in patients with data at Analysis Visit Month 48	Integrated ITT - PS Extended Common Support Region
DIST_PSWEIGHTS_48M_MISSING	Distribution of PS weights in patients without data at Analysis Visit Month 48	Integrated ITT - PS Extended Common Support Region

Abbreviations: ITT – Intention-to-treat; PS – Propensity score

All the distributions evaluated are not suggestive of a different allocation of weights that would be a driver for bias. There are little grades of variability in the shape of some distributions, with slightly different level of kurtosis and skewness, but these can be ignored considering the small samples and the number of subgroups analysed.

The company would like to highlight that we did not give priority to any of the studies integrated as discussed during the EAG technical meetings. Hence the weights have been automatically assigned by the PS algorithm just considering the prognostic factors overall, in line with the Statistical Analysis Plan.

A2. Priority question. Please, provide further detail on the application of propensity score weighting in the integrated analysis. Specifically:

a. **For each study, please provide:**
    i. **the number of patients, for each arm of every trial, who experienced spontaneous recovery during follow-up; and**
    ii. **density plots for distribution of weights assigned to these patients.**
b. **Please clarify if any sensitivity analyses were conducted to assess the potential impact of high-weights (i.e., the 10% greatest patient weights),**

imputed cases on the treatment effect estimates. If so, please describe these sensitivity analyses.

c. **Where available, please provide any tabulated results or study level breakdowns that support the responses to the above questions.**

Due to the limited time allowed to reply to this question, the company decided to provide the information in tabular format. Summaries have been produced for all the populations and strata requested in terms of frequency of patients, total sum of weights, and percentiles: 5th, 10th, 25th, 50th, 75th, 90th and 95th. Results are contained in the following outputs:

Output	Title	Population
DIST_PSWEIGHTS_CRR6	Distribution of PS weights in patients with CRR at Analysis Visit Month 6	Integrated ITT - PS Extended Common Support Region
DIST_PSWEIGHTS_CRR12	Distribution of PS weights in patients with CRR at Analysis Visit Month 12	Integrated ITT - PS Extended Common Support Region
DIST_PSWEIGHTS_CRR24	Distribution of PS weights in patients with CRR at Analysis Visit Month 24	Integrated ITT - PS Extended Common Support Region
DIST_PSWEIGHTS_CRR36	Distribution of PS weights in patients with CRR at Analysis Visit Month 36	Integrated ITT - PS Extended Common Support Region
DIST_PSWEIGHTS_CRR48	Distribution of PS weights in patients with CRR at Analysis Visit Month 48	Integrated ITT - PS Extended Common Support Region

Abbreviations: ITT – Intention-to-treat; PS – Propensity score

The company are not able to comment on these results since the intention of the investigation requested by EAG is unclear. The CRR is a variable correlated with treatment group, as demonstrated by the statistically significant treatment effect for idebenone clearly shown in the analysis models. Correlation of CRR with other prognostic variables, that are part of the derivation of the weights, has also been demonstrated. Hence, commenting on the difference in the distributions of weights by treatment arm and CRR occurrence would not be appropriate. The same is applicable to the distribution among the studies, since most of them include only one treatment arm.

In line with the Statistical Analysis Plan, our analysis included only the observations within the extended common region, i.e. patients with weights outside the region in

common to both treatment groups are automatically excluded. No sensitivity analysis has been conducted, since any selection of patients would affect the distribution of the PS weights and selected prognostic factors in an arbitrary way. The main request following the previous committee meetings was to obtain a better balance in terms of prognostic factors between the treatment groups, and the current analysis is aimed at addressing that concern without adding any external bias.

With regards to 'spontaneous recovery' it is important to contextualise this. Any improvement in VA from nadir in an untreated patient is labelled 'spontaneous recovery' but this is typically only a slight improvement in VA in a small percentage of patients. The mechanism of action of this effect is unknown & may be subtly different from the MOA of idebenone. Rather than reactivating viable but dormant retinal ganglion cells it could be the plasticity of the brain adapting to the new reduced capacity and recruiting cells normally utilised for peripheral vision to restore a degree of central, detailed vision. It is impossible to differentiate this effect in treated patients.

A3. Priority question. Please provide further details on the contribution of RHODOS vs CaRS studies to the 6-month treatment effect estimate. Specifically:

a. **How many patients from each study contributed data to the 6-month timepoint in the weighted analysis?**
b. **Please provide a comparison of the weights assigned to RHODOS patients and CaRS patients at the 6-month timepoint;**
c. **Based on the weight assigned to RHODOS in the integrated analysis compared to the observational studies, comment on the importance of this RCT informing early treatment effect estimates compared to the observational studies.**

Due to the limited time allowed to reply to this question, the company decided to provide the information in tabular format. Summaries have been produced for all the populations and strata requested in terms of frequency of patients, total sum of weights, and percentiles: 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th} and 95^{th}. Results are contained in the output DIST_PSWEIGHTS_6M_PRESENT.

Output	Title	Population
DIST_PSWEIGHTS_6M_PRESENT	Distribution of PS weights in patients with data at Analysis Visit Month 6	Integrated ITT - PS Extended Common Support Region

Abbreviations: ITT – Intention-to-treat; PS – Propensity score

The distributions evaluated are not suggestive of a different allocation of weights that would be a driver for bias. There are some small grades of variability in the shape of some distributions, with slightly different level of kurtosis and skewness, but these can be ignored considering the small samples and the number of subgroups analysed.

The company consider it of high importance to use RCT data to inform early treatment effects compared to observational studies. Hence why in previous cost-effectiveness analyses performed by the company, the data from RHODOS RCT only were used to inform the treatment effects of idebenone verses SoC from baseline to month 6, with observational studies used to inform long-term effects, whether this was using a naïve comparison or a propensity score weighted analysis (PSWA).

However, the EAG and NICE raised uncertainties over not incorporating the full integrated analysis dataset, using all available RCT and observational studies, from baseline for the weighted analysis. Hence why the company have now performed the updated weighted analysis presented as part of the response to DCG2.

A4. Priority question. The EAG is concerned that the company has not presented the results of the weighted integrated analysis at 6 months alongside all other time points from month 12 onwards. As such, please provide the results of the 6-month weighted analysis for idebenone vs SoC.

Company response

The company have presented the weighted integrated analysis results at month 6 and these are presented in Table 7 of the Company's DCG2 response alongside the outputs of the economic model at each time point.

If the EAG are referring to Table 3, Table 4 and Table 5 of the DGC2 response not presenting results of the change in BCVA in LogMAR at month 6, this is due to the

results reported in those tables being derived using a mixed model of repeated measures (MMRM) approach. As described in the Statistical Analysis Plan, the MMRM approach assumes linearity that cannot be postulated for the period before 12 months (Table 3 of the DCG2 response). As a sensitivity analysis, the above model was also rerun on the imputed datasets as per MAR and MNAR approach described in the Statistical Analysis Plan and used to derive the transition probabilities (Table 4 and Table 5 of the DCG2 response). As no linearity was assumed before month 12, the change in BCVA in logMAR at month 6 was not provided in these tables but instead derived via descriptive stats based on direct logMAR assessments and presented in Table 7 of the DCG2 response.

A5. Priority question. In the earlier LEROS Natural History (NH) matched analysis, the company stratified patients by time since onset (>1 year after the onset of symptoms and ≤1 year after the onset of symptoms). Given the large discrepancy in mean time since symptom on-set (and baseline LogMAR values) between the integrated analysis and many of the studies, as presented in the table below, please could the company clarify how time since onset was treated in the current propensity score-weighted integrated analysis? Specifically:

a. **The LEROS NH matched analysis provided in the LEROS CSR was performed for subgroups based on whether a patient had a time since onset of <= 1 year or >1 year, with differing results reported for these subgroups. In contrast, the analysis subsequently provided by the company, both here and at ACM2, did not separate patients by time since onset. As such, please can the company elaborate on why subgroup analyses were not performed for patients with a time from onset of <=1 year and >1 year given the potential confounding treatment effects identified in the stratified LEROS NH matched analysis outcomes. Additionally, please can the company outline why it was considered appropriate to include time since onset as a continuous variable (as opposed to a discrete variable) in the matching analyses given that patients in these subgroups are known to have very different disease progression pathways?**

b. **Please report if the company explored whether using time since onset as a categorical variable (as in the LEROS NH matched analyses) would lead to different results?**
c. **Please provide a breakdown of the distribution of patient weights or propensity scores stratified by ≤1 year vs >1 year time since onset.**

Study	Mean months since symptom onset (SD) [range]	Mean baseline logMAR (SD)
Integrated analysis (Idebenone & SoC patients)	Idebenone patients - [redacted] ([redacted]) SoC patients - [redacted] ([redacted])	Idebenone patients - [redacted] ([redacted]) SoC patients - [redacted] ([redacted])
RHODOS (Idebenone & SoC patients)	23 (16.2) [2-62]	1.59 (0.62)
CaRS I (SoC patients only)	3.6 (4.8)	0.696 (0.61)
CaRS II (SoC patients only)	3.4 (5.6) [0 - 48.1] 95.4% of patients were ≤ 1 year since 1st symptom onset at BL	0.65 (0.61)
LEROS (Idebenone patients only)	18.4 (15.8) [0.26 - 58.3]	1.15 (0.6)
PAROS (Idebenone patients only)	67.94 (97.842) [0.4 - 591.8]	0.928 (0.64)

EAP (Idebenone patients only)	4.6 (3) [0.3 -11.5]	1.23 (0.52)

a. As per Statistical Analysis Plan, the time from onset has been included in the PS algorithm along with the other prognostic variables. Subjects have been weighted to balance differences among the treatment groups overall and not within each study. Moreover, the time from onset has been included as covariate within the MMRM, the logistic regression model on CRB, and the multiple imputation algorithm, to adjust results on treatment effect from confounding factors and possible residual unbalance. Hence, there is no risk that the results are biased by the distribution of the time from onset.
The current knowledge of the disease and its management is continuously evolving and, thanks to the generation of data, both fresh from new studies and from new analyses of current data, we are now in a position to understand the disease better. For many years (until the 2017 Consensus), the disease was classified as acute or chronic (following in some way the medical concept that “something that stays long enough is considered chronic”).[1] Together with that concept, the experts considered that 12 months since onset of symptoms would provide a point to differentiate late recovery from acute visual dysfunction in the LEROS study (initiated in 2016).
However, already by 2017, four different stages of LHON had been identified: asymptomatic, subacute (<6 months from onset), dynamic (6-12 months from onset), chronic (<12 months from onset), thereby already introducing a differentiation within the group of patients diagnosed from less than 12 months.
After that date, new publications have highlighted that within each disease phase, the course of LHON is different.
In the EU PAR, an ancillary analysis showed how within the chronic patients, differences are observed in different subgroups of disease duration.[2]
In a poster presented at EVER 2014, based on data extracted from CRS-1 it has been shown how the visual acuity values during the first 12 months can

be very different in the natural history, and that values close to month 12 are not comparable to the ones during the first 6 months.[3]

The selection of a continuous variable rather than a categorical variable is therefore due to the acknowledgment that the course of the disease is very different within disease duration categories. In the months immediately after symptom onset there is a rapid deterioration in visual acuity, which can take a few weeks or a few months until the nadir is reached. After that, natural history patients will either stabilise at the nadir or there may be a degree of spontaneous recovery. The timing of this deterioration, stabilisation or spontaneous recovery is highly variable amongst the patient population. Once a patient has reached nadir any recovery is most likely to occur in the subsequent months which may still be within or right after the first year from onset. Taking all these known factors collectively a continuous variable is more reflective of the disease state than a binary distribution around a year. Classifying patients by time from onset <=1 year and >1 year would have missed these differences. The understanding of LHON is an evolving one and we are constantly juggling how to make best use of the available, often imperfect data. LEROS is a valuable piece of evidence but should be judged in context with other data sources.

b. However, as per EAG request, the PS algorithm has been run considering time from onset as categorical variable. The results are contained in the output PS_MODEL_FULL_TIMEGR. Results about inclusion of patients and variance of the propensity score are comparable with the main PS model. The weighted MMRM model has also then been run considering the time from onset as a categorical variable. Results are contained in the output MMRM_WEIGHTED_FULL_TIMEGR. Results are consistent with the main model submitted, with very little variation in results at each timepoint.
Please note: the model failed to converge due to hessian positive matrix. A compound symmetric covariance matrix has been selected instead of an unstructured one. A possible explanation for this is that the categorization <=1 year, >1 year has failed to adequately capture the variation of the patients due

to this prognostic factor. Not being able to explain enough variance that was not already captured by other effects, it has created multi collinearity.

c. The distribution of the weights by time from onset considering the categorization <=1 year and >1 year is provided in output DIST_PSWEIGHTS_TIMEGR. The distributions are well aligned. The group of SoC patients with time from onset > 1 year has a more right skewed distribution but given the considerations above and the adjustment done considering the time from onset as continuous variable this is not deemed as a risk of bias.

Output	Title	Population
PS_MODEL_FULL_TIMEGR	PS Model - Stabilized ATE Weights - Extended Common Support - Gender, Age at First Onset, Time from First Onset at Bsl as Categorical Variable (<=1 year; >1 year), Bsl Best BCVA, Eyes Involved at Bsl, Mutation. Reference Period.	Integrated ITT
MMRM_WEIGHTED_FULL_TIMEGR	Weighted MMRM - Change from Bsl in Best BCVA - 6 Month Analysis Visits: 12,18,24,30,36,42,48 months.	Integrated ITT - PS Extended Common Support Region
DIST_PSWEIGHTS_TIMEGR	Distribution of PS weights by time from onset as categorical variable. PS model run with time from onset as continuous variable.	Integrated ITT - PS Extended Common Support Region

Abbreviations: ITT – Intention-to-treat; MMRM – Mixed model of repeated measures; PS – Propensity score

A6. The EAG has aimed to gather the number of patients in each study from the relevant CSR materials as presented in the table below. The EAG has totalled the number of patients across all studies to 1,166, which is 86 patients fewer than that reported in the company's most recent submission (1,252). Please can the company correct the table below to highlight which patients are missing and provide the sources that can be used to validate the incorrect values.

Study	Study participants	Participants excluded from the integrated analysis	Participants included in the integrated analysis
RHODOS	85	13	72

CaRS-I	368	184	184
CaRS-II	203	11	192
EAP	111	55	56
PAROS	203	124	79
LEROS	196	18	178
Total	1,166	405	761

The company is unclear from where the numbers in the above table have been taken from. In our submission of the integrated analysis, the following table has been included:

Study Identifier	Intent-To-Treat Population Flag		
Frequency	**N**	**Y**	**Total**
SNT-CRS-002	11	208	219
SNT-EAP-001	55	56	111
SNT-II-003	13	82	95
SNT-IR-006	184	201	385
SNT-IV-003	124	104	228
SNT-IV-005	18	196	214
Total	405	847	1252

The total number of patients reported in the last column aligns with the number of patients reported in study reports and the sum is 1,252 as per our submission. Below are the sections and the sentences where these numbers can be verified in each clinical study report.

- SNT-CRS-002:Patient Data Collection: “Data from a total of 219 patients were obtained for the study.”

- SNT-EAP-001: Synopsis, Patients and Clinical Centres: “111 patients were enrolled in the EAP at 38 centres”
- SNT-II-003: Figure 5: Patient Disposition: “Screening (95)”
- SNT-IR-006: Patient Disposition: “A total of 383 CRFs containing the results of 3128 VA assessments were received”. Two additional patients have been included in the integrated dataset since the demographic data have been collected, however no visual acuity has been collected, hence excluded from the ITT population.
- SNT-IV-003: Abstract, Subjects and Study Size, Including Dropouts: “The study enrolled 228 patients (1 patient requested all data to be removed and therefore this patient was discounted from the number of originally enrolled 229 patients)”
- SNT-IV-005: Figure 1: “Assessed for eligibility (n=214)”

A7. Table 1 in the company’s most recent submission describes the baseline characteristics of the patients included in the PSM analysis. This table includes the variable ‘patient baseline best visual improvement in terms of logMAR’. Please can the company confirm if this variable should instead be labelled baseline best visual acuity. If the variable is correctly labelled, please can the company;

a) Provide a definition for this variable including how it differs from baseline best visual acuity;
b) Why this variable has been included;
c) Why best visual acuity was not included;
d) Provide baseline best visual acuity between the integrated analysis treatment arms.

Company response

The company can confirm that the labelled variable in Table 1 of the DCG2 is a typographical error and should instead state “Baseline best visual acuity (LogMar), mean (SD)”.

A8. Please can company share the following documents;

- The CaRS I CSR;

- The slide deck shared with the clinical experts whose opinions are reflected in Appendix C of the company's most recent submission.

Company response

- The CaRS I CSR has been sent as a separate reference as part of the company's response to these clarification questions and has been resubmitted through NICE Docs for convenience.
- The slide deck shared with the clinical experts as part of Appendix C is already provided as an appendix at the bottom of Appendix C.

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model ("ModelSettings" tab). If scenarios cannot be implemented as user selectable options, please supply instructions on how to replicate the scenario. Furthermore, if the company chooses to update its base case analysis, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base case assumptions are provided with the response along with a log of changes made to the company base case.

B1. Priority question. The EAG considers that the idebenone treatment effect is intrinsically linked to time on treatment. Given the company's preference for informing treatment discontinuation in the model using time to indicate treatment discontinuation, please can the company justify their base case approach of adjusting time on treatment with no reciprocal adjustment to treatment effects?

The EAG appreciates the company's opinion that in clinical practice patients may be prescribed treatment over a shorter duration given the learnings of the company's clinical trials. However, the studies used to inform the integrated analysis treatment effects did not include a stopping rule. The EAG therefore considers that employing a stopping rule with no consideration of how the

treatment may be affected introduces bias in favour of idebenone to the cost-effectiveness results, and is therefore inappropriate.

Company response

The company would like to firstly clarify that there is no evidence to date that once patients have responded & plateaued in terms of VA that there is any additional benefit in continued treatment. Nor is there any evidence that once treatment has been discontinued that patients regress. Hence the cost-effectiveness model & proposed treatment is in line with this and expert clinical opinion.

The company wish to reiterate that LHON is a rare disease and therefore limitations in the available data exist and are to be expected. Despite these data limitations, the data used to inform the clinical effectiveness of idebenone compared to SoC, via the weighted analysis, are strong and can accurately inform long-term clinical effectiveness. Whilst the company acknowledge that some uncertainties still exist within the weighted analysis, it is the best use of all data that the company has available to them and is the most suitable approach to modelling clinical effectiveness compared to all other alternative approaches.

The company have made extensive efforts to address the uncertainty presented by the data limitations raised by the EAG and NICE, including creating a whole integrated analysis and running two separate propensity score weighted analyses (PSWA) as part of the ACD1 and ACD2 responses, and seeking clinical expert validation on multiple occasions in order to validate the assumptions and outputs of the various iterations of analyses.

The company appreciate that there is uncertainty by employing a treatment stopping rule with no reciprocal adjustments to treatment effects, however, the company are severely limited by the data available for idebenone as a licenced rare disease product and the approaches required to model the long-term treatment effects.

There is a large amount of missing data and, as per the company's approach, data is imputed in the long-term after 12 months making it very difficult and sometimes impossible to assess and match the treatment effect of patients who would be assumed to stop treatment due to lack of response or by achieving a CRR. The

company did carefully consider how clinical effectiveness could be affected when introducing the time to indication to treatment discontinuation guidelines, however, the limitations in the current data analysis does not make it possible to run alternative scenarios.

However, the company do only assume that patients transition for up to 36 months in the base-case analysis. In the time to indication to treatment discontinuation KM curve, there are still [redacted]% of patients on treatment at 18 months, [redacted]% of patients on treatment at 24 months, and although no patients transition after month 36, [redacted]% of patients are still assumed to be receiving treatment after 36 months up until 54 months. In comparison, in the EAG's base-case, patients are not assumed to transition after month 48, however, the time to treatment discontinuation curve used still assumes that [redacted]% of patients are still receiving treatment at month 60, [redacted]% of patients are still receiving treatment at month 72 and [redacted]% of patients are still receiving treatment at month 108, despite no treatment effectiveness being reflected in the transition probabilities. This can be considered heavily biased against idebenone and a gross misrepresentation of how idebenone would be administered in clinical practice.

By the design of the RHODOS and LEROS clinical studies, patients who stop treatment at either month 6 or month 24, respectively, and are censored in the KM estimates, are also lost to follow-up, meaning their assessments will be imputed as part of the derivation of the transition probabilities. Assuming the company's base-case assumption of the missing not at random (MNAR) approach, their assessments will be imputed assuming a SoC-equivalent effectiveness which does not suggest a bias in favour if idebenone. However, evidence demonstrates that these patients who do stop treatment earlier maintain their treatment benefits in the long-term. For example, the benefit of idebenone was maintained in the off-medication period between RHODOS and RHODOS-OFU (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 (n=85) to RHODOS-OFU (n=58) favouring idebenone.[4] 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).[4]

For those patients in the clinical studies where there is a longer follow-up duration, such as the EAP study, by definition of the time to indication to treatment duration criteria they would only stop treatment if they had achieved no clinically relevant recovery (CRR) within 24 months or if they have achieved CRR and had plateaued. Therefore, it is not expected that the contributed assessments of these patients to the transition probabilities would demonstrate any treatment benefit in favour of idebenone.

Therefore, the company strongly believe that the clinical effectiveness reflected in the economic model for idebenone is reflective of clinical practice even when incorporating the time to indication to treatment discontinuation criteria.

Furthermore, presented in OUTPUT_10 of the updated Statistical Analysis Report 2025 provided to the EAG on 29th May 2025 are the weighted baseline characteristics of the idebenone arm at baseline, month 6 and month 12 but also the number of patients included at each of the timepoints. At baseline there are N=[redacted] idebenone patients, at month 6 there are N=[redacted] patients and at month 12 there are N=[redacted] patients include. In the time to indication to treatment discontinuation there are N=[redacted] patients at risk at baseline, N=[redacted] patients at risk at month 6 and N=[redacted] patients at risk at month 12. This suggests that a similar number of patients who were continuing to contribute to the clinical effectiveness in weighted analysis to derive the transition probabilities were still contributing to the treatment duration analysis. From month 12 onwards, due to the multiple imputation under the MNAR approach those patients who were lost to follow-up were assumed to experience SoC effects which is a conservative assumption if they were still receiving treatment.

As per NICE guidelines, the company considered the most accurate way to model time on treatment so that it would most reflect clinical practice and have extensively consulted with clinicians on this matter. As part of the company's clinical validation (Appendix C of the DCG2 response, April 2025), clinical experts were consulted on the company and EAG's approach to modelling time on treatment. Both clinicians strongly agreed that most patients would be off treatment by 36 months with one

clinician stating that "[redacted]% was an appropriate proportion of patients who would likely remain on treatment after 36 months, and that she does not expect this percentage to exceed 1-2%". The clinician further highlighted that the company's time to indication to treatment discontinuation curve "provided a more coherent and realistic representation of clinical practice" compared to the time to treatment discontinuation curve adopted by the EAG. The clinician also stated that "in her experience, she had observed some patients who showed continued improvement in VA up to 24 months, but by 36 months, she had not seen any patients continuing treatment beyond that point". This observation was consistent with the findings of another clinician who stated that "most patients would be off treatment by 36 months, with very few patients on treatment more than 36 months and that any patients taking up to or more than 5 years is exceedingly rare and that all patients should be off treatment within 4 to 5 years".[5]

Following this clinician consultation, the company conducted informal discussions with clinical experts to form informal treatment 'guidelines' to understand exactly how clinicians expect to treat patients in clinical practice, for which conclusions, provided in the company's DCG2 response, aligned with the company's proposed time to indication to treatment discontinuation.

Therefore, the company consider that the most appropriate approach has been taken to model the treatment duration of idebenone in the company base case whilst using the best available data for modelling long-term clinical effectiveness and not misrepresenting the treatment effects.

References

1. Carelli, V. *et al.* International Consensus Statement on the Clinical and Therapeutic Management of Leber Hereditary Optic Neuropathy. *Journal of Neuro-Ophthalmology* **37**, 371–381 (2017).
2. EMA. Raxone (idebenone) European Public Assessment Report. (2015).
3. Metz, G. *et al.* A case report survey (CRS) on the natural history of visual acuity in patients with Leber's hereditary optic neuropathy (LHON). *Acta Ophthalmologica* **92**, 0–0 (2014).
4. NICE. Single Technology Appraisal Idebenone for treating visual impairment in Leber's hereditary optic neuropathy in people 12 years and over [ID547] Committee Papers. (2024).
5. Chiesi Farmaceutici S.p.A. Appendix C. Clinician Validation Report. (24th April 2025). (2025).

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

ACM 3 - EAG report

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This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136145.

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].

Table 1 presents a brief overview of the key issues identified by the EAG as being potentially important for decision making. Table 2 presents EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 2 of this report details the EAG critique of the company's most recent submission of clinical evidence and economic model, explaining the EAG's key issues in more detail.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	Inappropriate weighting of baseline characteristics in the company's propensity score weighting analysis	3.1.1 and 3.1.3
3	Indication to time to discontinuation is inappropriate	3.2
4	Lawrence *et al.* HUI-3 utilities are inappropriate[1]	3.4

Abbreviations: EAG, External Assessment Group; HRQoL, Health related quality of life; PSA, probabilistic sensitivity analysis, SoC, Standard of care

Table 2. EAG's preferred model assumptions

Scenario	Incremental costs	Incremental QALYs	ICER (£)	Change from company base case (£)
Company base case	[redacted]	[redacted]	28,241	—
Integrated analysis TTD	[redacted]	[redacted]	53,129	+24,888
Lawrence *et al.* EQ-5D utility values[1]	[redacted]	[redacted]	40,368	+12,127
Carer disutility applied as an absolute value	[redacted]	[redacted]	28,928	+687

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TTD, time to treatment discontinuation.

2 Executive summary

The External Assessment Group (EAG) outlines in Section 2 of this report their response to the company's submission of additional evidence, following the draft guidance published post appraisal committee meeting (ACM) 2.

Despite the company performing an integrated analysis pooling all data sets across the available Leber's Hereditary Optic Neuropathy (LHON) studies, and using a propensity score weighted analysis (PSWA) to mitigate imbalances in prognostic factors between data sources (Section 3.1.1), the EAG continues to have concerns about the robustness of the results.

The EAG notes that the company did not analyse data up to 6 months using a mixed model for repeated measures (MMRM), similar to subsequent time points, due to concerns about linearity assumptions being inappropriate before month 12, given the rapid deterioration in Baseline Best Corrected Visual Acuity (BCVA). However, alternative statistical methods (e.g. descriptive regression, non-linear MMRMs) that could allow a more comparable result with subsequent time points were not explored. This limits confidence in the comparability and robustness of the integrated analysis results and reduces transparency in how RHODOS data informs early treatment effect estimates (see Section 3.1.1).

The EAG is concerned that the large loss of patient numbers over time, and hence the large proportion of imputed data, may have impacted the robustness of the treatment effect estimate. The EAG notes that although imputation methods were performed, the loss of data was striking, particularly after month 24. The EAG acknowledges that LHON, being a rare disease, can impact the availability of patient data, but considers that the results should still be interpreted with caution (Section 3.1.2).

In particular, the EAG notes that the integrated analysis includes substantial variability in time since first symptom onset, a key prognostic factor in LHON. While the weighted mean time since onset is similar between arms ([redacted] vs [redacted] months for idebenone vs standard of care [SoC], respectively), the standard deviations are very large ([redacted] and [redacted] months. In contrast, the medians differ more substantially ([redacted] vs [redacted] months), indicating a non-normal distribution) indicating that the mean values are heavily skewed by outliers, which raises concerns about the appropriateness of mean-based weighting (discussed in Section 3.1.3).

Given the heterogeneity in time since symptom onset and disease stage (indicated by the wide range of time since symptom onset), the EAG considers that relying on mean values in propensity score weighting may not adequately account for between-arm differences. While the integrated analysis includes patients across a range of disease stages, the particularly long mean time since onset, large standard deviations and upper ranges, and the contribution of LEROS and PAROS to the idebenone arm, suggest that the population is more reflective of a prevalent population (i.e. chronic LHON patients). These concerns, discussed further in Section 3.1.3, raise questions about the face validity of the weighted baseline characteristics and whether the integrated analysis is reflective of the incident population typically eligible for treatment in clinical practice.

The EAG also highlights that the integrated analysis combines data from studies with divergent baseline profiles, particularly in time since symptom onset (with the SoC arm predominantly informed by early-stage patients form CaRS-I and CaRS-II and the idebenone arm mostly informed by later stage patients from LEROS and PAROS), which may introduce bias not fully addressed through statistical adjustment.

While the EAG acknowledges that it could be argued that the imbalance in time since onset could bias results in favour of SoC, since patients in the early phase may be more likely to experience some spontaneous recovery, it is also important to consider that early onset patients may present with a steeper decline in visual acuity, particularly if they are recruited prior to the nadir phase. As a result, the overall impact of this imbalance is difficult to predict with certainty. The EAG considers that this reinforces rather than undermines the need for caution in interpreting treatment effects, as the imbalance in disease stage introduces uncertainty and undermines comparability across arms, particularly given that time since onset is a strong prognostic factor affecting visual outcomes.

In light of these concerns, the EAG believes that stratifying patients by time since symptom onset, rather than weighting, would have been a more clinically valid approach.

The EAG notes that the company has previously conducted a matched analysis using idebenone patients from the LEROS study and SoC patients from the CaRS I and CaRS II studies, stratifying by time since onset (≤1 year vs >1 year). This approach ensured a closer alignment of disease trajectories and offered a more clinically appropriate comparison. Furthermore, the patient populations in the LEROS CaRS matched analysis substantially overlap with those used in the integrated analysis, and yet produce very different results, further supporting the necessity of

comparing findings across these two approaches (results are presented and discussed in Section 3.1.4).

Clinical importance of time since symptom onset

EAG clinical experts advised the EAG that time since symptom onset in LHON is an important prognostic factor that can impact treatment effectiveness. Visual loss typically follows a course of: rapid deterioration over several months, reaching a nadir around 4 to 6 months and stabilising by 6 to 12 months post-onset.[2, 3] Patients treated with idebenone earlier, particularly within the first year of onset, consistently show better chances of recovery. For example, idebenone administered within one year of vision loss is associated with stabilisation or improvement of visual acuity, whereas chronic cases treated later on show variable outcomes.[4-7] Clinical expert consensus and the available evidence support early treatment initiation, reinforcing the importance of stratifying by time since onset in analyses, as early treatment initiation can correlate with a more favourable response to treatment.

In this context, the incident population typically refers to those patients are within one year of symptom onset, representing the subacute or dynamic phases of the disease when visual loss may still be evolving. On the other hand, the prevalent population is generally those patients more than one year post-onset, often in the chronic phase of the disease, where visual acuity has stabilised and the likelihood of treatment response/spontaneous recovery is lower.[8] The EAG notes this is a clinically meaningful distinction that underpins the rationale for evaluating treatment effects separately by disease stage.

3 EAG critique

3.1 Evaluation of the integrated analysis and treatment effects

To address the methodological concerns raised by the EAG over the company's previously presented integrated propensity score weighted analysis (PSWA), which instead of including the RHODOS RCT directly in the analysis, had the results of the RHODOS RCT naively dovetail with the integrated analysis in the economic model, the company performed an updated integrated PSWA incorporating all available clinical data (including the RHODOS RCT data) to inform the treatment effect of idebenone and standard of care (SoC).

The updated integrated analysis incorporated all available clinical data (RHODOS, RHODOS-OFU, EAP, CaRS-I, CaRS-II, LEROS and PAROS) for both idebenone and SoC, with a PSWA conducted to mitigate imbalances in prognostic factors between patients from different data sources.

3.1.1 Propensity score weighting analysis

The company's PSWA was conducted by calculating one weight for each patient for the full intention to treat (ITT) population of the analysis, from baseline through to month 48. The EAG considers this to be a reasonable approach.

The following baseline variables were incorporated into the propensity score (PS) model as regression factors:

- Sex;
- Age at onset;
- Time from onset at baseline;
- Baseline Best Corrected Visual Acuity (BCVA);
- Unilateral/Bilateral involvement at baseline;
- Type of mutation (i.e., G11778A, G3460A, T14484C).

Patients with missing data on these covariates were excluded. Similarly to the company's previous PSWA, visual acuity at nadir, highlighted as an important prognostic factor for LHON by the EAG's clinical experts, was not included in the current analysis. The EAG recognises it was not possible to obtain data for this variable from the included registry studies but considers this omission a limitation of the current PSWA.

While the company provided assessment graphs including weight clouds and standardised mean differences, the EAG identified limitations in their interpretability. For example, in the plot showing time from first onset at baseline (Figure 1 below), most data points are clustered below 100 months while the x-axis extended to 600 months, obscuring any distribution differences. Moreover, despite weighting, the box plot indicated a remaining difference in median time since onset between arms (see Section 2.1.3 for further discussion). The EAG noted that the unweighted median difference between idebenone ([redacted] months) and SoC ([redacted] months), was [redacted], and may be of particular important given the known differential efficacy of early vs late treatment in LHON. A notable difference of [redacted] remained after weighting (median of [redacted] for idebenone and [redacted] for SoC). However, this difference was not easily visible in the box plot.

Figure 1. Time (months) from first onset at baseline (reproduced from the company's ISA Report: PS Model- Time from First Onset at baseline. Integrated ITT (output 6)

The EAG noted that the information the company provided as part of their response was not sufficient to assess whether the weights were appropriately distributed and raised further clarification questions for the company. Specifically, the EAG requested that the company provide density plots for the weights assigned to patients (across populations, studies, treatment arms and timepoints). Instead, the company provided summary statistics detailing the total sum of weights and weights at the 5th, 10th, 25th, 50th, 75th, 90th and 95th percentiles for each of the requested populations. The minimum or maximum weights for each of the requested populations were omitted. The rationale for the EAG requesting density plots was to allow assessment of the weighted populations for skewedness, kurtosis, or the influence of outliers, factors which could bias the

results. Accordingly, in the absence of density plots, this was not possible for the EAG to assess using the data provided by the company.

In response to a clarification question, the company asserted that the distributions were not suggestive of bias but did not provide sufficient supportive data. Although the company's response indicates that density plots, at least for some of the requested populations, were available and reviewed internally and the company stated that there were no concerns with regards to kurtosis and skewedness, the impact of potential outliers (i.e., patients assigned particularly large weights) was not discussed. Accordingly, the EAG remains concerned that outliers within the weighted analyses may have unduly influenced the results.

In addition, the EAG was concerned that although the company reported conducting a weighted analysis including RHODOS (the only available RCT) patients at month 6, the results of this analysis were not presented. This limits the EAG's ability to compare treatment effect estimates between the period where evidence included RCT patients and later time points where RHODOS patients were no longer followed up and multiple imputation had been performed. Consequently, the EAG could not evaluate whether the inclusion of RHODOS patients influenced early treatment effect estimates, particularly given their potentially different baseline characteristics (e.g. time since onset and baseline logMAR; see Section 2.1.4) or assess the consistency of treatment effects over time and determine whether observed long-term benefits are maintained once RHODOS patients are no longer contributing data. Therefore, the EAG requested that the company provide these results.

In their response to clarification, the company stated that 6-month results have been presented in Table 7 of the company's response, but the EAG notes this is using a logistic model for missing at random (MAR) and missing not at random (MNAR) scenarios covering the economic model as well as the integrated analysis. The company clarified that 6-month data were excluded from tables presenting change in best BCVA in logMAR derived from the integrated weighted analysis using MMRM, MAR and MNAR approaches because MMRM assumes linearity, which the company claims is inappropriate before month 12 due to rapid BCVA deterioration.

The EAG notes that the company chose not to run the MMRM for month 6 due to concerns about linearity assumptions, but they did not explore alternative statistical methods (e.g. descriptive regression, non-linear MMRMs) that could allow a more comparable result. Since MMRM was applied to all other timepoints, not applying it to month 6 limits comparability and leads to a lack of

consistency across analysis time points. As previously raised by the EAG prior to ACM 2, the company may have instead accounted for any non-linearity by implementing non-linear MMRMs.[9]

The EAG requested weighted analysis for idebenone vs SoC at 6 months but Tables 7 and 8 in the company's DG2 response only give within arm change for idebenone and SoC, respectively, not between arm differences, which would allow the EAG to better understand the treatment effect.

Thus, while the company has provided weighted 6-month results per arm in Tables 7 and 8, this does not fulfil the request for a direct, transparent comparison between idebenone and SoC at 6 months using the same methods of analysis applied at later time points (i.e. MMRMs). As such, the EAG is still unable to assess the relative treatment effect at the only time point where RHODOS (the only RCT) contributes fully to the analysis. This limits confidence in the comparability and robustness of the integrated analysis results and reduces transparency in how RHODOS data informs early treatment effect estimates.

3.1.2 Modelling approaches and missing data

To overcome the issue of missing data, the company used multiple imputation in the analyses performed from 12 months onwards. The company used a MMRM to estimate treatment effects under two different imputation assumptions: MAR and MNAR. Sensitivity analyses using both assumptions, alongside the weighted with the implicit MAR were presented and MNAR was used as the company's base case.

The EAG notes that multiple imputation was only performed from 12 months onwards. As shown in Table 3 below, the number of patients with available data declines rapidly over time with a substantial decrease observed after month 24 in the idebenone arm (from 205 to 58 patients) and after month 12 for SoC arm (from 113 to 59 patients).

The EAG notes that this pattern of attrition, particularly the greater and earlier drop-off in the SoC arm, may introduce bias if the missingness was associated with factors such as disease worsening or loss to follow-up due to lack of improvement. While multiple imputation was used, the large volume of missing data at later time points means that estimates beyond month 24 rely increasingly on imputed values rather than observed data. Moreover, the differential rate of missing data between treatment arms complicates the interpretation of comparative effects. With only 58 idebenone patients and 33 SoC patients remaining at month 30, and fewer than 40 per arm by month 42, the results at later time points are likely to be much less robust. The EAG therefore considers that

conclusions drawn from analyses beyond month 24 should be interpreted with caution, particularly in light of the increasing reliance on imputed data and the limited observed patient population.

Table 3. Number of missing and included patients in the integrated analysis (reproduced from Table 17 of Appendix D in the company's DG2 response)

	Baseline	Month 6	Month 12	Month18	Month 24	Month 30	Month 36	Month 42	Month 48
Number of patients included									
Idebenone	402	374	285	243	205	58	53	30	37
SoC	437	260	113	59	55	33	33	32	116
Number of missing patients									
Idebenone	0	28	117	159	197	344	349	372	365
SoC	0	177	324	378	382	404	404	405	321
Proportion of patients missing									
Idebenone	7%	29%	40%	49%	86%	87%	93%	91%	7%
SoC	41%	74%	86%	87%	92%	92%	93%	73%	41%

Abbreviations: SoC, standard of care

In addition, the EAG notes that data from the integrated analysis at months 42 and 48 were excluded due to small sample sizes, specifically citing 30 patients in the idebenone arm and 32 in the SoC arm at month 42. However, the company does not clearly define or justify the threshold used to determine when a sample size is deemed too small for inclusion.

This is particularly relevant given that only 58 idebenone patients and 33 SoC patients remained at month 30, and 53 idebenone patients vs 33 SoC patients at month 36. These sample sizes, although not substantially larger than those at month 42 were still included in the analysis. The criteria used to justify exclusion at later time points may thus have been inconsistently applied and not transparently reported, raising concerns about potential *post hoc* decisions that could influence conclusions about treatment effectiveness over time.

The EAG therefore considers that the lack of a clear, pre-specified threshold for acceptable sample size may undermine the transparency of the analysis and may introduce selection bias in the time points retained for primary interpretation.

3.1.3 Baseline characteristics

The baseline characteristics of the matched patients from the integrated, weighted analysis including RHODOS are presented in Table 4 below.

Table 4. Baseline characteristics from the weighted analysis (adapted from Table 1 in the company's DG2 response and Table 14 in the EAG report)

Parameter		Weighted analysis		RHODOS (ITT)	
		Idebenone	SoC	Idebenone	SoC
Gender	Male, (%)	[redacted]	[redacted]	85.5	86.7
	Female, (%)	[redacted]	[redacted]	14.5	13.3
Mutation	G11778A	[redacted]	[redacted]	67.3	66.7
	G3460A	[redacted]	[redacted]	12.7	13.3
	T14484C	[redacted]	[redacted]	20	20
	Other	[redacted]	[redacted]	-	-
Laterality	Bilateral	[redacted]	[redacted]	NR	NR
	Unilateral	[redacted]	[redacted]	NR	NR
Analysis age (at first onset), mean (SD)		[redacted]	[redacted]	NR	NR
Time from first on set at baseline (months), mean (SD)		[redacted]	[redacted]	22.8 (16.2)	23.7 (16.4)
Baseline best visual improvement (LogMAR), mean (SD)		[redacted]	[redacted]	1.61 (0.64)	1.57 (0.61)

Abbreviations: ITT, Intention-to-Treat; logMAR, logarithm of the minimum angle of resolution; SoC, standard of care

The EAG notes certain areas where baseline differences may undermine the comparability of treatment arms and the reliability of the treatment effect estimate.

While the majority of patients were male, the proportion was relatively lower compared to patients in the RHODOS trial, which the EAG's clinical experts consider to more accurately reflect clinical practice across studies included in the clinical evidence for idebenone. However, the EAG has no concerns that this discrepancy is likely to have considerably influenced the treatment effect.

The EAG notes that the proportion of patients with m.11778G>A mtDNA mutation, which is associated with a poorer prognosis and a lower probability of spontaneous recovery, broadly matched but was slightly lower than that of patients in the RHODOS trial. The EAG also notes that the distribution of the other two most prevalent mutations, m.14484T>C and m.3460G>A, differed to that of RHODOS (20.0% across arms for m.14484T>C and 12.7% vs 13.3% for m.3460G>A in idebenone and placebo patients, respectively) and that contrarily to the current analysis, in the RHODOS trial the prevalence of m.14484T>C was higher compared to m.3460G>A, which is associated with the greatest probability of spontaneous visual recovery.[10] Nevertheless, the EAG notes that although the impact of those discrepancies is unclear, the distribution of mutations was matched between the idebenone and SoC arms of the current weighted analysis.

Furthermore, the EAG notes that weighted mean time (months) from first onset was higher in the integrated analysis compared to the RHODOS trial. While the weighted mean time since onset appears broadly similar between arms ([redacted] vs [redacted] months for idebenone vs SoC, respectively), the standard deviations are large ([redacted] and [redacted] months respectively), suggesting that the mean values are highly skewed by extreme values. Thus, the EAG is concerned that this may undermine the reliability of the means as a summary statistic in the population in this analysis.

The EAG considers that such wide variability in time from first onset may obscure true differences in patient characteristics between arms. This concern is further reinforced by the median values ([redacted] months for idebenone and [redacted] months for SoC), which differ more substantially than the means and suggest non-normal distributions. This raises concerns about the appropriateness of mean-based weighting. Given this heterogeneity, the EAG considers that reliance on a mean-based approach may be misleading as it may not adequately account for the differences between arms.

In addition, the wide range of time since first onset ([redacted] to [redacted] for idebenone vs [redacted] to [redacted] for SoC) suggests the sample included patients across various stages of the disease from the subacute, acute to dynamic and chronic phases of LHON. Considering that visual recovery is more likely during the early stage of the disease, this heterogeneity may have influenced the treatment effect estimate.

Baseline logMAR values also reflect this variability. The mean time from first onset being >1 year in the weighted population and the mean baseline best logMAR being almost 1 suggest that most patients in the integrated analysis were most likely representative of prevalent LHON patients in the chronic phase of the disease and less likely to be in the earlier subacute/acute and dynamic phases. This may not adequately reflect the incident population typically eligible for treatment in clinical practice, where patients are more likely to start treatment in earlier disease stages. The EAG considers this may indicate an important limitation, especially as time since symptom onset is a crucial prognostic factor in LHON, which can influence treatment effectiveness. While the integrated analysis includes patients across a range of disease stages, the EAG notes that the particularly long mean time since onset, the large standard deviations and upper ranges, and the contribution of LEROS and PAROS to the idebenone arm, suggest that the population is overall, more reflective of prevalent (i.e. chronic) LHON patients.

Given the large discrepancies between the idebenone and SoC time since first symptom onset, the EAG considers that stratifying the integrated analysis data by time since first symptom onset or

weighting the patient observations around the median time since first symptom onset instead of using the mean time would have been a more appropriate approach.

The EAG notes that in a previous analysis conducted by the company, idebenone patients from the LEROS study were matched to natural history patients from the CaRS-I and CaRS-II studies, with the results stratified according to whether time since first symptom onset was greater or less than one year. In the LEROS CaRS matched analysis, for patients with ≤1 year since symptom onset, the mean time since symptom onset was [redacted] and [redacted] months, with baseline logMAR being [redacted] and [redacted] for idebenone and SoC arms, respectively. The EAG notes that these mean times since symptom onset are more reflective of the median values ([redacted] and [redacted] months, respectively) and the baseline logMAR values are aligned with those of patients treated in clinical practice according to the company's clinical experts. Similarly, for patients with >1 year since symptom onset, mean time since symptom onset was [redacted] and [redacted] months, with baseline logMAR being [redacted] and [redacted] for idebenone and SoC arms, respectively, and are much more reflective of the corresponding median values for months since symptom onset ([redacted] and [redacted]) compared to the integrated analysis.

The EAG also notes that the CaRS studies contributed approximately 93% of patients to the SoC treatment arm in the integrated analysis (and 100% of patients after six months), while LEROS contributed the largest proportion of patients to the idebenone arm of the integrated analysis (51% at baseline, increasing after six months as RHODOS patients are no longer followed up). While the majority of patients informing the integrated analysis are from the LEROS CaRS matched analysis, the outcomes of the matched and integrated analyses differ considerably. A detailed comparison of outcomes from the matched and integrated analyses is presented in Section 3.1.4.

The EAG highlights that the integrated analysis combines data from studies with divergent baseline profiles. The SoC arm is informed predominantly by CaRS-I and CaRS-II studies (46% and 47%, respectively), which included patients early in disease progression i.e. reflecting an incident population, while the idebenone arm is mostly informed by LEROS (51%) and PAROS (27%), where patients were typically in later stages i.e. representing a prevalent population. As a result, the use of propensity score weighting across such heterogeneous populations, particularly for time since onset, may introduce bias that is not fully addressed through statistical adjustment.

Imbalances are evident in both the unweighted and weighted baseline characteristics, further highlighting the challenges in achieving population comparability across treatment arms and the

importance of assessing whether the PSWA has sufficiently addressed baseline imbalances between treatment arms.

For example, in the SoC arm, the mean time since first symptom onset was [redacted] months, while the median was only [redacted] months, indicating a skewed distribution likely influenced by a small number of patients with very long durations. The maximum time since onset reported in the integrated analysis for the SoC arm was [redacted] months, which could not be validated by the EAG, against CaRS study data, where the maximum was 48 months and most patients had <1 year since onset. The EAG considers that the use of the PSWA across studies with such divergent disease trajectories and baselines, particularly regarding time since first symptom onset, may introduce bias not fully addressed by statistical adjustment.

The LEROS CaRS matched analysis was considered more clinically plausible, as it directly accounted for the influence of time since onset, an important prognostic factor in LHON.

The EAG notes that the LEROS CaRS matched analysis matched patients based on disease timing, i.e. time from symptom onset and VA measurement intervals ensuring better clinical comparability of patients. While the integrated PSWA adjusts for a wider set of prognostic factors, it does so statistically rather than through strict clinical matching. As a result, it is less tailored to the disease trajectory. This introduces a risk of confounding, especially given the concerns over time since symptom onset outlined above (also see Section 2) and particularly since included covariates do not fully capture disease factors like timing of nadir.

The EAG therefore considers the LEROS CaRS matched analysis more clinically plausible and so more appropriate for estimating the treatment effect at early time points. This is because:

- It only includes two studies (LEROS CaRS datasets) with comparable follow-up procedures and greater clinical alignment in terms of time since symptom onset;
- The matching algorithm aligns patients by visual acuity windows (e.g. +/- 3 months), ensuring comparability in the timing of baseline assessments;
- It avoids the temporal mismatch seen in the integrated analysis, where discrepancies in mean vs median time since onset (e.g. [redacted] vs [redacted] in the SoC group) reduce face validity.

Hence, the EAG considers the LEROS CaRS matched analysis to provide a more clinically valid estimate reflective of real-world treatment effects.

While acknowledging limitations of the LEROS CaRS matched analysis, including its smaller sample size compared to the integrated analysis, lack of adjustment for mutation type and shorter follow-up (up to 24 months), the EAG notes the identified limitations of the integrated analysis that included:

- A high proportion of imputed data from 24 months onwards;
- Poor face validity of baseline covariates (mean and median time since symptom onset differ substantially, especially in the SoC arm);
- Heterogeneity across studies contributing to each arm: SoC is informed mostly by CaRS (early onset), and idebenone by LEROS and PAROS (late onset), which results in a mismatch in disease stage between arms that weighting may not account for, especially given the high proportion of imputed data;

For these reasons, the EAG concludes that the LEROS CaRS matched analysis is more appropriate, offering better clinical comparability, better alignment on time since onset and avoiding many of the other biases and uncertainties associated with the integrated analysis.

3.1.4 Results of the integrated analysis

3.1.4.1 Integrated analysis

For the analysis of change in BCVA in logMAR, three different modelling approaches were performed, discussed in Section 2.1.2. An MMRM, with implicit imputation of missing values under a MAR assumption, was chosen as the company's preferred analysis and this was performed on all ITT patients after month 12. However, as a sensitivity analysis, the model was rerun on the imputed datasets using a MNAR approach, which the EAG considers to be the least biased of the two options and which formed the company's base case in the economic model.

An adjusted estimate of the mean change from baseline in best BCVA was derived for each visit and the model included treatment group, analysis visit, treatment-by-analysis-visit interaction, sex, age at onset, mutation, time from onset at baseline, best BCVA at baseline as fixed effects and baseline best BCVA-by-analysis-visit interaction weighted by the stabilised inverse probability of treatment weights computed by the PS model.

The MMRM analysis produced estimates for 6-month intervals from month 12 to month 48.

The estimated change from baseline in BCVA in logMAR and the estimated difference in BCVA in logMAR for idebenone and SoC from baseline using MNAR assumption are presented in Table 5, below.

Table 5. Change in BCVA in logMAR derived from the integrated analysis as measures by the MMRM analysis - MNAR (reproduced from Table 5 in the company's DG2 response)

Analysis visit	Estimated change in logMAR ± SE (95% CI)		Estimated difference in logMAR	P-value
	Idebenone	SoC	Idebenone vs SoC	
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]
Month 30	[redacted]	[redacted]	[redacted]	[redacted]
Month 36	[redacted]	[redacted]	[redacted]	[redacted]
Month 42	[redacted]	[redacted]	[redacted]	[redacted]
Month 48	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA, Best corrected visual acuity; CI, Confidence interval; logMAR, Logarithm of the minimum angle of resolution; MNAR, missing not at a random; MMRM, Mixed models for repeated measure; SE, Standard error; SoC, Standard of care

The EAG notes that, as demonstrated by the results of the MMRM model, at month 12 there is an estimated mean worsening with a change from baseline logMAR of [redacted] for the MNAR assumption for the idebenone group and [redacted] for the SoC group. The between-group difference of [redacted], which is equivalent to an improvement of [redacted] letters on the ETDRS. The analysis was statistically significant in favour of idebenone ([redacted]).

Similar results were observed in subsequent time points at month 18 and month 24 as the between-group difference remains statistically significant in favour of idebenone at both time points. However, the magnitude of the benefit appears to be gradually decreasing over time.

At month 36, the estimated mean change in logMAR for the SoC group shows a decrease compared to month 30, suggesting a slowing in the rate of visual deterioration, but the between group difference in favour of idebenone remains statistically significant. However, the EAG notes that as highlighted in Table 3, the number of patients with available data is substantially reduced after month 24 compared to previous time points and this may have affected the robustness of the treatment effect estimates.

Although not used in the economic model, the company also provided the results for month 42 and month 48. There was a statistically significant difference between the idebenone and SoC groups in the long-term, suggesting patients treated with idebenone continue to see a clinical benefit compared to SoC, although the magnitude of the effect slightly declines. However, the EAG notes the greatly reduced number of patients upon which the estimated treatment effects were based.

Overall, the EAG notes that under MNAR assumption, logMAR values for idebenone at most time points are higher and the differences in treatment effect are smaller. However, idebenone still appears to show a significant benefit over SoC, although with a reduced magnitude compared to the earlier time points, indicating that while idebenone may slow visual deterioration, its benefit decreases over time.

3.1.4.2 PSWA compared to LEROS CaRS matches analysis

In light of the concerns raised previously, the EAG draws attention to the results of the LEROS CaRS matched analysis stratified by time since symptom onset (≤1 year vs >1 year). These are presented in the Table 6 alongside the results of the PSWA analysis, under the MNAR assumption.

Table 6. Best BCVA in logMAR results of the integrated PSWA and the LEROS CaRS matched analysis (derived from LEROS Appendix 14.2)

	Mean logMAR		Change from baseline		Difference in change from baseline between treatments
	Idebenone	SoC	Idebenone	SoC	
Integrated PSWA					
Baseline	[redacted]	[redacted]	-	-	-
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LEROS CaRS matched analysis: first symptom onset ≤ 1 year					
Baseline logMAR	[redacted]	[redacted]	-	-	-
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LEROS CaRS matched analysis: first symptom onset > 1 year					
Baseline logMAR	[redacted]	[redacted]	-	-	-
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PSWA, propensity score weighted analysis; SoC, standard of care.

As presented in Table 6, at six months the between treatment group difference in change in logMAR from baseline in the integrated PSWA analysis is considerably greater compared to the LEROS CaRS matched analysis ([redacted] vs [redacted] and [redacted] in the integrated PSWA vs the matched analysis ≤1 year and >1 year subgroups, respectively). Similarly, while in the integrated PSWA the difference in treatment effects is sustained (from [redacted] at six months to [redacted] at 24 months), in the LEROS CaRS matched analysis, the difference in change from baseline in patients with first symptom onset ≤1 year was [redacted] at 24 months. In patients with first symptom onset of >1 year, the between-treatment group difference in change at 24 months was [redacted], which is more reflective of the integrated PSWA difference of a [redacted]. However, the EAG notes that in absolute terms, SoC logMAR in the LEROS CaRS matched analysis was [redacted] at month 24, which was [redacted] to the mean idebenone logMAR of [redacted]. In the time since symptom onset of >1 year matched analysis, [redacted] in logMAR were measured between the treatment arms across any time point.

The EAG notes that the logMAR trajectory in the integrated PSWA aligns with that of the LEROS CaRS matched analysis for patients with first symptom onset of ≤ 1 year. At six months in the integrated analysis, SoC logMAR was estimated to increase by [redacted] compared to baseline. Comparatively, in the

LEROS CaRS matched analysis, smaller increases in logMAR of [redacted] and [redacted] were noted for patients with symptom onset of ≤ 1 year and >1 year, respectively.

The EAG notes that the MMRM models show the largest and clearest benefit for idebenone compared to both LEROS CaRS matched analysis subgroups. At 24 months, the LEROS CaRS matched analysis shows a smaller benefit. However, both arms appear to decrease i.e. improve in logMAR over time, although the treatment difference is bigger in the integrated PSWA. The EAG considers that the integrated PSWA may overestimate the early benefit of idebenone because it does not stratify by symptom onset.

Therefore, the benefit of idebenone is more evident in the MMRM-based integrated PSWA. As noted earlier, given that the integrated PSWA and the LEROS CaRS matched analysis largely overlap in terms of the patients informing them, yet they produce substantially different results, with the integrated PSWA showing a greater benefit for idebenone compared to the more conservative LEROS CaRS matched analysis. The EAG considers that the methodological differences between the two analyses are likely to be causing the change in treatment effect. Thus, the EAG is concerned that this undermines the robustness of the results as they are highly sensitive to the modelling approach used. The EAG considers the LEROS CaRS matched analysis to be more clinically appropriate as it better controls for time since symptom onset, a major prognostic factor.

Given the comparable changes in logMAR between the integrated analysis and the LEROS CaRS matched analysis for patients with ≤ 1 year since first symptom onset, and considering that patients in the LEROS CaRS matched analysis may have been more clinically appropriately matched than in the PSWA (given the better alignment in baseline logMAR and time since first symptom onset), the EAG conducted a scenario analysis using the LEROS CaRS matched analysis treatment outcomes. As the EAG only had access to the baseline and mean logMAR values, in order to conduct the scenario, the EAG estimated normal distributions of patients across the model health states that would provide a mean logMAR equal to that recorded in the LEROS CaRS matched analysis. In the scenario, time to treatment discontinuation was aligned with the treatment administration from the LEROS study, with approximately 73% of patients remaining on treatment for two years, and all patients discontinuing treatment after three years. The scenario led to an increase in the ICER with model outcomes presented in 4. For completeness, the EAG also conducted a scenario using the LEROS CaRS matched analysis outcomes for patients with first symptom onset greater than one year which showed a greater ICER then the less than one year symptom onset patients.

3.2 Time on treatment

As assumed at ACM 2, in the company's updated economic model, time on treatment was informed using the indication to time to treatment discontinuation. The indication to discontinuation was estimated by the company using time to discontinuation from the integrated analysis and applying assumptions to reflect when the company's clinical expert patients would expect to stop treatment in clinical practice. The EAG notes the considerable difference between time to discontinuation with and without the company's additional assumptions (Figure 2 and Figure 3), and the significant reduction in idebenone treatment costs following the application of the indication to treatment discontinuation assumptions.

Figure 2. Integrated analysis - time to indication of treatment discontinuation

Figure 3. Integrated analysis - treatment discontinuation

The company's justification for preferring to inform the model using the estimated indication to time to discontinuation, in consideration of the ACM 2 discussions, is that the company remains confident that their treatment discontinuation estimates most accurately reflect the duration of treatment clinicians would expect to deliver in clinical practice. However, to further support the model's alignment with their clinicians' expectations, the company incorporated into the model the functionality to allow patients who continue to show improvement in VA to continue treatment beyond 36 months. In the company's scenario analysis, it was assumed that 2% of patients continued treatment for another two years (five years of total treatment), in accordance with the company's clinical expert opinions. The scenario had a small impact on the ICER, increasing the company base case cost-effectiveness results by £369.

While the EAG considers it probable that time to indication of discontinuation, as described by the company's clinical experts, may more accurately reflect time on treatment in future clinical practice, given the learning from the idebenone clinical trials; the company has failed to consider the intrinsic link between idebenone time on treatment and treatment benefits. Therefore, arbitrarily adjusting time on treatment according to the company's methodology only serves to introduce bias into the model outcomes in favour of idebenone by reducing the idebenone treatment costs with no reciprocal adjustment to treatment benefits.

It is the EAG's opinion that time to discontinuation from the integrated analysis is the most appropriate source to inform time on treatment in the model as it reflects the time over which idebenone patients may experience a direct treatment effect. However, the EAG acknowledges that

time to discontinuation from the integrated analysis contradicts the opinions of the company's clinical expert opinions. In particular, the EAG notes that the company's experts stated that "most people should be off treatment within four to five years". Comparatively, the integrated analysis recorded that approximately [redacted] of the at-risk patient population remained on treatment after five years in the integrated analysis.

The EAG has therefore conducted scenario analyses around the time on treatment in the model, when assuming the integrated analysis treatment effects. In the first scenario, the EAG assumed that after five years of idebenone, all patients would discontinue from treatment. In a second scenario, it was assumed that all censored patients from the integrated analysis treatment discontinuation data were assumed to have discontinued treatment (Figure 3). The indication to treatment discontinuation, treatment discontinuation and EAG scenario proportions of patients on treatment over time are provided in Figure 4.

Figure 4. Idebenone treatment discontinuation, integrated analysis and scenarios

Abbreviations: EAG, external assessment group; TTD, time to discontinuation.

Between the scenarios provided by the EAG, it is the EAG's opinion that assuming all patients discontinue treatment after five years is the more conservative assumption, given costs are accounted for all patients from which a treatment effect was measured over a longer period. With the latter scenario, censored patients may well continue treatment and incur treatment costs, thereby accounting for the treatment benefits without the treatment cost. This latter scenario, therefore, reflects a minimum treatment cost assumption with respect to the treatment effects.

As previously described, the EAG considers that time on treatment from the integrated analysis is the most appropriate source to inform treatment discontinuation in the model as it directly reflects the time over which patients benefitted from treatment. Time to discontinuation from the integrated analysis is therefore assumed in the EAG's base case assumptions. However, the EAG notes that the time to treatment discontinuation in the LEROS study, which is assumed in the EAG's scenario analyses using the LEROS CaRS treatment effects, is highly reflective of the company's preferred indication to time on treatment assumptions. As such, the EAG considers that if the indication to treatment discontinuation assumptions are preferred, the LEROS CaRS matched analysis treatment is the most appropriate source of treatment effects, given the alignment in treatment discontinuation (Figure 5).

Figure 5. Integrated analysis and LEROS time to discontinuation comparison

Abbreviations: TTD, time to discontinuation.

3.3 Caregiver health related quality of life

At ACM 2, the company included in their preferred modelling assumptions a disutility for carers of people with LHON who had a visual acuity of greater than logMAR 1 and were not living in residential care. The disutility applied was that identified by Wittenberg *et al*. 2013,[11] as previously used to inform the economic model for HST 11,[12] which provided guidance for treating inherited retinal dystrophies caused by genetic mutations. In the HST 11 EAG base case assumptions, a carer disutility was not included. HST 11 concluded that it was appropriate to apply a carer disutility for

parents of children with a condition that causes blindness; however, the disutility was not applied to carers of adults. Given the on-set of LHON in adulthood, a carer disutility was not therefore assumed. Overall, the committee for HST11 concluded that, "*The EAG's approach of excluding disutility values for carers of adults in all health states could be appropriate, but it could consider scenarios including a carer disutility for adults with LHON if more quantitative evidence for carers of adults with LHON or other conditions that cause blindness was provided*".

In the present company's submission and economic model for ACM 3, a carer disutility has again been assumed for all patients with a logMAR above one who do not live in residential care. In this instance, the company has supported this assumption using the findings of Ahmadu *et al.* 2025,[13] which used the outcomes of a survey conducted by the LHON Society. In the survey, LHON patients reported on relying on an average of 1.58 carers for 24.8 out of 31 days per month, reflecting a need for assistance 83% of the time or an average of 1.3 carers for continuous support. The company considered that the study highlighted the critical role caregivers play in the lives of patients and the impact on caregivers' quality of life.

The EAG was unable to validate the methods of the study as the reference provided was that of a poster, which lacked the details around the survey and the assessment of results. However, the poster did report findings around the impact on carer quality of life (QoL), with 50% of responders reporting a severe impact to QoL, 36% reporting a moderate impact on QoL, and 75% experiencing increased anxiety. Without understanding how these metrics have been calculated, it is unknown how well the reported QoL reflects health related quality of life (HRQoL) as is appropriate for health technology appraisals; however, the EAG notes that anxiety is one of the EQ-5D dimensions and therefore considers that the company has provided evidence to support plausibility of an assumption of applying a carer disutility in the model.

Following the findings of Ahmadu *et al.*,[13] the carer disutility in the economic model has been updated to reflect the continuous need for 1.3 carers, with the applied disutility being the product of the disutility (0.04) and the number of continuous carers required (1.3), as measured in the LHON Society's survey. It is the EAG's understanding that carer disutility is measured as a shared burden between carers, and as such, it is inappropriate to apply care disutility on a per carer basis. Therefore, in the EAG base case, a care disutility has been included, but as the absolute value (0.04) and not as the product with the estimated number of required continuous carers.

3.4 Health state utility values

In the company's updated economic model, health state utility values (HSUVs) have been informed using the Lawrence *et al.* 2025 HUI-3 values,[1] as they were in the company's previous model. However, the EAG considers the Lawrence *et al.* EQ-5D utility values to be more appropriate and are assumed in the EAG base case.

From the ACM 2 published draft guidance, the company's reasonings for preferring the HUI-3 values included that; "*HUI-3 utility values were more appropriate and in line with previous NICE technology appraisal guidance for measuring health related quality as compared with EQ-5D*" and "*HUI-3 contains a vision component while EQ-5D is known to have poor convergent validity in visual disorders"*. Alternatively, the EAG preferred the EQ-5D values as "*EQ-5D is used as a standard for deriving utility for QALYs, ensuring consistency across evaluations".*

From the company and EAG differing opinions the committee concluded that, "*Although the EQ-5D measurement method is preferred to measure health-related quality of life in adults. It recalled that, in some circumstances the EQ-5D may not be the most appropriate measure. To make a case that the EQ-5D is inappropriate, qualitative empirical evidence should be provided on the lack of content validity for the EQ-5D, showing that key dimensions of health are missing as described in NICE's manual on health technology evaluation. No empirical evidence was presented by the company. But the committee recognised the difficulties in the ability to collect or generate clinical evidence in a rare condition and determined that it would consider HUI-3 utility values in its decision making. The committee concluded that, in this case, it would consider utility values generated using the HUI-3."*

The EAG agrees with the committee and the company that in some instances EQ-5D may not be an appropriate measure for conditions related to sight deterioration; however, in this instance the EAG considers the EQ-5D values to be appropriate as was determined by the EAG and committee in HST11.

While the EAG agrees with the company that the EQ-5D dimensions do not include a visual component, the EAG disagrees with the company's opinion that there is poor convergence between the Lawrences *et al.* EQ-5D values and visual decline. Presented below are the Lawrence *et al.* HSUVs in addition to the other utility values explored by the company in scenario analyses, informed by the precedents in previous appraisals (Csozki-Murray *et al.* 2009 in TA298,[14] Rentz *et al.* 2014 in HST 11[15]) and the company targeted literature review (Brown *et al.* 1999[16]).

From the HSUVs, the EAG considers that the utility decline associated with loss of visual acuity in the Lawrence *et al.* EQ-5D utilities to be comparable to that from other sources used in previous appraisals. As such, the EAG considers there to be a high level of consistency between visual decline and utilities estimated using the EQ-5D dimensions.

Table 7. Vision related health state utility values

	Brown *et al.*[16]	Lawrence *et al.* EQ-5D-5L[1]	Lawrence *et al.* HUI-3[1]	Lawrence *et al.* TTO[1]	Czoski-Murray[17]	Rentz *et al.* (UK only)[15]
LogMAR <0.3	0.84	0.79	0.84	0.88	0.71	0.92
LogMAR 0.3-0.6	0.77	0.63	0.51	0.76	0.68	0.85
LogMAR 0.6-1.0	0.67	0.57	0.44	0.70	0.51	0.80
LogMAR 1.0-1.3	0.63	0.50	0.35	0.57	0.51	0.72
LogMAR 1.3-1.7	0.54	0.50	0.33	0.53	0.31	0.69
CF	0.52	0.37	0.21	0.41	0.31	0.53
HM	0.35	0.35	0.19	0.43	0.31	0.38
LP	0.35	0.34	0.18	0.36	0.31	0.26

Abbreviations: CF, counting fingers; HM, hand movement; LP, light perception; TTO, time trade off.

From Table 7 the EAG notes that the HUI-3 values are the most pessimistic utilities, reflecting the steepest utility declines between health states and the lowest utility values for the off-chart sight health states. The Lawrence *et al.* EQ-5D and Czoski-Murray values are the second most pessimistic for on-chart health states, with the Rentz *et al.* utilities presenting the sharpest decline in off-chart health states.

The EAG considers that the HUI-3 values are potentially oversensitive to visual decline, given the high difference in HRQoL between health states compared to the other sources of utility. As presented in Table 7, the decrement in HRQoL between the logMAR <0.3 and LogMAR 0.3-0.6 health state is -0.33 (from 0.84 to 0.51). In terms of visual decline, this represents going from being able to read standard print to struggling in low light and potentially requiring visual aids. The associated

estimated disutility for this level of sight decline is double that measured by Ara and Brazier 2010[18] for patients experiencing a stroke (-0.164). Similarly, the HUI-3 utilities associated with off-chart blind health states are comparable to those measured in end stage terminal cancers by Pourrahamt *et al.* 2021.[19]

Based on these comparisons, it is the EAG's opinion that the HUI-3 utilities are overly sensitive to visual acuity decline and their use introduces bias in favour of the more effective treatment, given the steep decline in HRQoL between health states and the low HRQoL values associated with off-chart sight heath states. The EAG considers that the Lawrence *et al.* EQ-5D values show a comparable level of utility decline following vision decline to utility sources used in previous relevant appraisals. For these reasons the EAG has assumed the Lawrence *et al.* EQ-5D HSUVs in the EAG base case.

4 EAG scenario analyses and base case results

Table 8 presents the outcomes of the EAG's scenario analyses as discussed in sections 3.1 and 3.2. Table 9 outlines the EAG's preferred base case modelling assumptions, used to inform the EAG's base case results as presented in Table 10.

The EAG has also provided alternative EAG base cases (Table 11), which assume differing treatment effects and times to treatment discontinuations from the EAG base case. In these base cases, the Lawrence *et al.* EQ-5D utilities[1] are assumed and the carer disutility has been applied as an absolute disutility.

Table 8. Results of the EAG's scenario analyses

#	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
0	Company base case	[redacted]	[redacted]	28,241
1	Replicating the LEROS CaRS matched analysis treatment effects for people with time since first symptom onset of ≤1 year	[redacted]	[redacted]	50,078
2	1 & LEROS TTD	[redacted]	[redacted]	45,196
3	Replicating the LEROS CaRS matched analysis treatment effects for people with time since first symptom onset of >1 year	[redacted]	[redacted]	95,329
4	3 & LEROS TTD	[redacted]	[redacted]	86,570
5	TTD - all patients discontinue treatment after five years	[redacted]	[redacted]	41,828
6	TTD - all censored patients are assumed to have discontinued treatment	[redacted]	[redacted]	33,139
7	Carer disutility applied as an absolute value	[redacted]	[redacted]	28,928

Abbreviations: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years; TTD, time to discontinuation.

Table 9. EAG preferred modelling assumptions

Preferred assumption	Independent ICER (£/QALY)	Cumulative ICER (£/QALY)
Company base case	28,241	-
Integrated analysis TTD (without additional assumptions)	53,129	53,129
Lawrence *et al.* EQ-5D utilities[1]	40,368	75,943
Carer disutility applied as an absolute value	28,928	78,609

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TTD, time to discontinuation.

Table 10. EAG base case

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]	78,609
Probabilistic results							
SoC	[redacted]	-	[redacted]	-	-	-	-
Idebenone	[redacted]	-	[redacted]	[redacted]	-	[redacted]	79,393

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SoC, standard of care.

Table 11. Alternative EAG base cases

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
LEROS CaRS matched analysis: time since first symptom onset ≤1 year & LEROS TTD							
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	68,471
LEROS CaRS matched analysis: time since first symptom onset >1 year & LEROS TTD							
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	132,012
Integrated analysis treatment effects & TTD: all patients discontinue treatment after five years							
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	61,903

Integrated analysis treatment effects & TTD: all censored patients assumed to have discontinued treatment							
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,033

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SoC, standard of care; TTD, time to discontinuation.

5 Conclusion

Overall, given the issues identified by the External Assessment Group (EAG) with the company's propensity score weighting analysis (PSWA), the EAG considers that the LEROS CaRS matched analysis may be more appropriate than the company's newly presented integrated PSWA for assessing the treatment effect of idebenone vs standard of care (SoC). It is the EAG's opinion that the matched analysis provides better clinical comparability, appropriate matching of time since onset and avoids the clinical heterogeneity and patient imputation issues of the integrated analysis. While the integrated analysis includes patients across a range of disease stages, the EAG notes that the particularly long mean time since onset, the large standard deviations and upper ranges, and the contribution of LEROS and PAROS to the idebenone arm, suggest that the population is overall, more reflective of prevalent (i.e. chronic) LHON patients. While the integrated analysis may offer longer-term data and a larger sample size, its methodological weaknesses (heterogeneous studies, potentially inappropriate weighting, and a large proportion of imputed data) undermine confidence in its results.

The EAG notes that while the integrated PSWA and the LEROS CaRS matched analyses are predominantly informed by the same patients, they produce very different results. The matched analysis presents a more modest difference in treatment effects between the idebenone and SoC than the integrated PSWA, with the early logMAR decline of SoC patients in the integrated analysis mirroring that of patients with symptom onset of less than one year in the matched analysis. The EAG is therefore concerned that the methodology used in the integrated PSWA may be amplifying the treatment effect or introducing bias through reliance on imputed data, and inconsistencies in disease stage, reflected in time since symptom onset and lack of stratification by disease stage (early vs chronic).

With respect to the time on treatment assumptions, the EAG considers that the time to treatment discontinuation in the model should reflect the time that patients were continuing to be treated in the integrated analysis. It is the EAG's opinion that treatment effects are intrinsically linked to time on treatment and that arbitrarily curtailing time on treatment with no reciprocal consideration to the impact on treatment effects introduces bias to the cost-effectiveness results in favour of idebenone. As the integrated analysis has been used to inform treatment effects in the company and EAG base case, the EAG considers the most appropriate treatment discontinuation source to be the integrated analysis, without the company's preferred assumption. However, the EAG notes that the

indication to treatment discontinuation values are highly reflective of patients who discontinued in the LEROS study. Therefore, if the indication to treatment discontinuation assumption is preferred, the EAG considers the LEROS CaRS matched analysis outcomes are most appropriate to inform treatment effects.

The EAG also considers that the company has provided sufficient evidence to support the inclusion of a carer disutility in the economic model. The company's supporting study, conducted by the LHON Society, recording a high reliance on carers by patients but also the considerable impact on carer QoL. As such, a carer disutility has been included in the EAG base case.

Lastly, in consideration of the company's opinion that EQ-5D is known to have poor convergent validity in visual disorders and that the HUI-3 utility values should be preferred; it is the EAG's opinion that there is considerable evidence to support the use of EQ-5D, given the alignment to utility used in vision loss related appraisals and the convergence of vision loss with utility decline. The EAG notes that compared to the other relevant sources of utility, the HUI-3 describes an extreme health-related quality of life decline with vision loss, with transition from good sight to struggling in low light, reflecting a similar decline in health-related quality of life as experiencing a stroke. Given the use of EQ-5D values in the NICE reference case and the comparability of the EQ-5D values to health state utility values used to inform relevant appraisals, the Lawrence *et al.* utility values have been used in the EAG base case.[1]

6 References

1. Lawrence C, Bojakowski S, Williams E, Lloyd A. Utility Estimates for Vision Loss in Leber Hereditary Optic Neuropathy POSTER CODE: PCR227. *Value in Health* 2023; **26**: SUPPLEMENT-S355.
2. Newman NJ, Carelli V, Taiel M, Yu-Wai-Man P. Visual Outcomes in Leber Hereditary Optic Neuropathy Patients With the m.11778G>A (MTND4) Mitochondrial DNA Mutation. *J Neuroophthalmol* 2020; **40**: 547-57.
3. Yu-Wai-Man P, Newman N, Carelli V, La Morgia C, Biousse V, Bandello F, et al. Natural history of patients with Leber hereditary optic neuropathy-results from the REALITY study. *Eye* 2022; **36**: 818-26.
4. Catarino C, von Livonius B, Priglinger C, Banik R, Matloob S, Tamhankar M, et al. Real-World Clinical Experience With Idebenone in the Treatment of Leber Hereditary Optic Neuropathy. *Journal of Neuro-Ophthalmology* 2020; **40**: 558-65.
5. Chen B, Newman N. Clinical trials in Leber hereditary optic neuropathy: outcomes and opportunities. *Current Opinion in Neurology* 2024; **38**: 79-86.
6. Newman N, Biousse V, Yu-Wai-Man P, Carelli V, Vignal-Clermont C, Montestruc F, et al. Meta-analysis of treatment outcomes for patients with m.11778G>A MT-ND4 Leber hereditary optic neuropathy. *Survey of Ophthalmology* 2025; **70**: 283-95.
7. Yu-Wai-Man P, Carelli V, Newman N, Silva M, Linden A, Van Stavern G, et al. Therapeutic benefit of idebenone in patients with Leber hereditary optic neuropathy: The LEROS nonrandomized controlled trial. *Cell Reports Medicine* 2024; **5**.
8. Carelli V, Carbonelli M, F. I, Kawasaki A, Klopstock T, Lagreze W, et al. International Consensus Statement on the Clinical and Therapeutic Management of Leber Hereditary Optic Neuropathy, 2017. Available from: https://journals.lww.com/jneuro-ophthalmology/fulltext/2017/12000/international_consensus_statement_on_the_clinical.5.aspx. Date accessed: 12 Jun 2025.
9. Gaccione P. Nonlinear Mixed Effects Models, a Tool for Analyzing Repeated Measurements A Brief Tutorial Using SAS Software, 1998. Available from: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://support.sas.com/resources/papers/proceedings/proceedings/sugi23/Stats/p228.pdf. Date accessed: 13 Jun 2025.
10. Yu-Wai-Man P, Chinnery PF. *Leber Hereditary Optic Neuropathy.* In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, et al., editors. GeneReviews((R)). Seattle (WA)2021.
11. Wittenberg E, Prosser LA. Disutility of Illness for Caregivers and Families: A Systematic Review of the Literature. *PharmacoEconomics* 2013; **31**: 489-500.
12. Nice. Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations. HST 11. NICE.
13. Ahmadu C, Roberts G, Mumford J, Mumford A. Association between caregiver quality of life and the care provided to adults with severe visual impairments: A systematic literature review, 2025. Available from: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.ispor.org/docs/default-source/cti-meeting-21021-documents/54d9cb9f-b55f-4b83-beee-4fdbb4c156a6.pdf?sfvrsn=249a1843_0. Date accessed: 11 Jun 2025.
14. Nice. Ranibizumab for treating choroidal neovascularisation associated with pathological myopia. TA298. 2013.
15. Rentz AM, Kowalski JW, Walt JG, Hays RD, Brazier JE, Yu R, et al. Development of a Preference-Based Index from the National Eye Institute Visual Function Questionnaire-25. *JAMA ophthalmology* 2014; **132**: 310-8.
16. Brown GC. Vision and quality-of-life. *Trans Am Ophthalmol Soc* 1999.

17. Czoski-Murray C, Carlton J, Brazier J, Young T, Papo NL, Kang HK. Valuing Condition-Specific Health States Using Simulation Contact Lenses. *Value in Health* 2009; **12**: 793-9.
18. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2010; **13**: 509-18.
19. Pourrahmat MM, Kim A, Kansal AR, Hux M, Pushkarna D, Fazeli MS, et al. Health state utility values by cancer stage: a systematic literature review. *Eur J Health Econ* 2021; **22**: 1275-88.