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:

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1. **Comments on the Draft Guidance** from Chiesi

2. **Company response to clarification questions on the draft guidance response**

3. **Consultee and commentator comments on the Draft Guidance** from:
   a. LHON Society, and patient experts James Ferguson and Lily Mumford

4. **Comments on the Draft Guidance received through the NICE website**

5. **External Assessment Group (EAG) critique of company comments on the Draft Guidance**

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10. **Updated results post error, provided by the EAG**

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

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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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 15 November 2024. 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? National Institute for Health and Care Excellence (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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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:**

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	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 Draft Guidance Consultation (DGC) document. The company is disappointed by the draft recommendation not to recommend idebenone. The company is keen to find a solution in partnership with NICE and National Health Service (NHS) England to enable 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 supportive treatments, does not prevent vision loss or allow recovery of visual function. Idebenone is the first and only licensed treatment option for visual impairment in adolescents and adults with LHON. Therefore, the company kindly requests that the committee reconsiders the negative draft recommendation to enable timely access to this clinically effective treatment. To aid the External Assessment Group (EAG) and committee in their decision-making, the company has provided a newly developed integrated analysis using all the available clinical data to inform the treatment effect of idebenone and SoC treatment, which has been incorporated into the cost-effectiveness model. This analysis, as well as any assumptions within the model, have been externally validated by UK clinicians. Additionally, the company has revised their base-case [redacted]. The company's revised base-case is £28,451 per quality-adjusted life year (QALY). **Key updates in this response to ensure appropriate committee decision-making:** • **Introduction of the integrated analysis set**: To address the lack of comparative data available between the idebenone and SoC arms, the company has created an integrated analysis set which incorporates all the available clinical data for both idebenone and SoC. From the integrated analysis dataset, a weighted analysis has been carried out to in order to inform the clinical effectiveness of both treatment arms and to accurately measure the value of idebenone compared to SoC. For more details on the integrated analysis and weighted analysis please see the company's response to Issue 1 in this response document. • **Update of the cost-effectiveness model:** Clinical efficacy from the integrated analysis was added to the cost-effectiveness model. Additionally, some assumptions were revised based on the first appraisal committee meeting (ACM1) discussion, DGC and the clinical validation. For more details, please see the company's response to Issue 2 in this response document. • **Clinician validation:** To validate the findings of the integrated analysis and obtain validation of the company's base-case assumptions the company conducted a clinical validation on October 17th, 2024. The outcomes of the integrated analysis set, including Best Corrected Visual Acuity, Clinically Relevant Benefit, and Time to Indication for Treatment Discontinuation were presented to clinicians. • [redacted]

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	[redacted] the revised company base-case incremental cost-effectiveness ratio (ICER) following changes at the DGC response is £28,451. [redacted], idebenone is a cost-effective use of NHS resources in an underserved population with a high unmet need. For more information, see the cost-effectiveness results in Table 10 of this DGC response.
1: Comparator data and establishing relative treatment effect	**An integrated analysis set using all available clinical data was created to ensure the most complete and robust dataset was used to inform clinical efficacy of both arms. The results of the analysis demonstrate a statistically significant mean change for almost all the analysis timepoints in best corrected visual acuity (BCVA) for idebenone vs SoC, in line with clinical practice as confirmed by clinical experts. Additionally, the results of the analyses demonstrate a substantial relative treatment benefit between idebenone and SoC which is sustained long-term, as supported by the statistically significant results of the estimated difference in logarithm of the minimum angle of resolution (LogMAR) and the odds ratio of the clinically relevant benefit (CRB) at each timepoint.** **<u>The company, EAG and committee's approaches at ACM1:</u>** Given the rarity of LHON and the only randomised controlled trial (RCT) comparing idebenone and SoC (RHODOS) being just 6 months long, there is limited clinical data available to inform the transition probabilities of the SoC arm and the long-term relative treatment effect of idebenone. At submission, the company used data from the RHODOS trial to inform the transition probabilities from baseline to 6 months in the economic model. To supplement the SoC data beyond 6 months, data from the case record survey (CaRS) were used and a naïve comparison was assumed between the Expanded Access Programme (EAP) study for the idebenone arm. It was assumed that the LogMAR visual acuity (VA) of patients remains unchanged after 36 months. The EAG criticised the use of the CaRS-I study alone to inform the SoC transition probabilities and highlighted that using CaRS-I and CaRS-II studies would have utilised all available data, and therefore provided a more complete estimate of the SoC treatment effect beyond month 6. Therefore, as part of the clarification questions (CQ's), the company conducted a scenario using both CaRS-I and CaRS-II datasets to inform the transition probabilities in the SoC arm, using the EAG's preferred model consisting of 4 health states, and removing SoC observations generated using last observation carried forward (LOCF), which decreased the ICER to £6,463. (EAG report 4.2.4.3).[1] As also requested from the EAG, the company performed a propensity score matching (PSM) analysis to compare the LEROS intention-to-treat (ITT) and full CaRS dataset (I and II) using a single baseline and 24-month visit window only. Given the substantial limitations of this PSM due to the small sample size and lack of consistent follow-up data in the CaRS-I and II study, the outputs of the PSM (change in best VA) were not reflective of the outputs seen in the LEROS trial and were deemed inappropriate for use within this appraisal. For example, no significant difference in best recovery of VA LogMAR or change in best VA from baseline to month 24 were shown in the PSM, but there is a significant benefit observed in the LEROS trial. Additionally, as found in LEROS, the estimated difference in CRB from baseline is statistically significant between both treatment arms at 24 months; 52.9% of eyes treated with idebenone achieve CRB at 24 months compared with 36% of eyes in the natural history (NH) group (odds ratio, OR: 2.082; p=0.0297).[2]

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	Furthermore, the outputs from the PSM could not be used to inform transition probabilities for SoC in the economic model due to the matching algorithm being performed *de novo* at each time point. This implies that the same patient is not necessarily followed over the trial duration as the matching was performed on eyes (not patients), and therefore, their movement across health states cannot be accurately captured. The EAG and committee concluded that the PSM did not provide reliable evidence of the long-term treatment benefit of idebenone compared to SoC. The company is aware of the uncertainty in the approach used to model the SoC arm in the submission base-case, however, all available data from the CaRS studies were used to inform transition probabilities. Therefore, the company remains confident that at the time of the original submission using RHODOS and CaRS data were the most appropriate data source to inform SoC clinical effectiveness and present a relative treatment benefit between SoC and idebenone. **Treatment benefit demonstrated in clinical studies** The company would like to highlight that the value of idebenone has been demonstrated throughout each clinical study and there is a clear treatment benefit compared to SoC. For example, in the EAP study, whilst 15.6% of eyes (n=27) treated with idebenone experience a clinically relevant recovery (CRR) at 6 months, this increases to 22.5% of eyes (n=39) at month 12, 28.3% of eyes at month 24 (n=49), and 29.5% of eyes at month 36 (n=51), demonstrating a clinically meaningful long-term treatment benefit.[3] Similarly, in the LEROS study, 42.3% of eyes treated with idebenone achieved CRB compared to the 20.7% of eyes in NH patients at month 12; this represents a 104% relative improvement compared to spontaneous CRB observed in NH eyes (statistically significant [p = 0.002]). This increases to 52.9% at month 24 in patients treated with idebenone, compared to 36% in NH patients (p=0.0297).[2] The results of the real-world evidence study and the single-arm trial demonstrates that idebenone does show a clear treatment benefit compared to SoC that is sustained long-term. **To aid in this response, the company has conducted an integrated analysis of all the available data** To address the uncertainties in both arms, an integrated analysis has been performed by the company by pooling all the data sets from different LHON studies (RHODOS, RHODOS-OFU, EAP, CaRS-I, CaRS-II, LEROS and PAROS). The data of 1,252 patients from these studies were included in the integrated datasets. Of these, 847 patients were included in the ITT population and 405 were excluded, with the main reasons for exclusion including no baseline data (N=159 patients) and no post-baseline data (N=70 patients). For a full list of the reasons for exclusion from the ITT population please refer to Table 15 in Appendix A. Of the patients included in the ITT population, 409 were analysed for the idebenone treatment group and 438 for the SoC treatment group, creating the biggest possible sample size available for the analysis. To address the EAG's and committee's concerns on the relative treatment benefit of idebenone versus SoC, a propensity score weighted analysis was also performed to mitigate any imbalance in prognostic factors between the treatment and SOC groups. Please see the attached statistical analysis plan (SAP) and the integrated analysis statistical report for further details on the analysis carried out.[4,5] In the integrated analysis, all efficacy analyses were derived based on the BCVA in LogMAR in the best-seeing eye (i.e best BCVA).

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Propensity score weighting analysis

One of the main limitations of an integrated analysis using data from different sources is the potential imbalance of prognostic factors between the treatment groups. To mitigate this limitation, a matching analysis was run, weighted by stabilised inverse probability of treatment weights computed by a propensity score (PS) model. The 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. For more detail on this please refer to the integrated analysis statistical report.[4]

As reported in the NH, 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. Hence, all the assessments included up to the 6-month analysis visit were analysed separately from the assessments included in the 12-month analysis visit onwards. For the analyses run on the assessments including the 6-month assessments, all assessments from the RHODOS study were excluded due to RHODOS being an RCT. In the cost-effectiveness analysis (CEA) RHODOS data are used to inform transition probabilities from month 0 to month 6.

Multiple imputation

To overcome the issue of missing data, within the efficacy analyses performed from 12 months analysis visit onward, a multiple imputation (MI) approach was used to assign a value to incomplete cases, i.e. best BCVA with missing data for a patient at an analysis visit. MI replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute. The multiple imputed datasets were then analysed using standard procedures for complete data, and the results from these analyses were combined.

Two different approaches were then adopted 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, that is, for a variable Y, the probability that an observation is missing depends only on the observed values of other variables, not on the unobserved values of Y.

- **MNAR:** In MNAR, a pattern-mixture model models the distribution of a response as the mixture of a distribution of the observed responses and a distribution of the missing responses. A control-based pattern imputation is applied, modelling post-withdrawal data from the idebenone treatment group as if they were from the SoC treatment group, or in other words, assuming that patients on the idebenone treatment group who withdraw will tend to have an efficacy trajectory similar to patients in the SoC treatment group.

Whilst no tests were carried out to determine if the data were MAR, the rarity of LHON and the nature of the NH study suggests that most of the data are MAR. However, both MAR and MNAR approaches were explored as part of the sensitivity analyses. 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.[4,5]

Mixed model for repeated measures

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The relative effectiveness of idebenone vs SoC was analysed based on the change from baseline in best BCVA using a mixed model for repeated measures (MMRM). An overall adjusted estimate of the mean change from baseline in best BCVA was derived that estimates the average treatment effect over visits giving each visit an equal weight. 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 with at least one assessment on or after 12-month analysis visit. 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 MAR and MNAR approach described above.

Outcomes from the integrated analysis

Baseline characteristics

The baseline characteristics of patients from the weighted analysis is presented in the table below (Table 1). Assessments in RHODOS-OFU were included for the SoC arm only. Idebenone patients from RHODOS-OFU were not included since they were no longer on treatment. As can be seen in Table 1, the baseline characteristics are well-balanced between the two treatment arms. Clinical experts validated these baseline characteristics on October 17th 2024, and agreed they are generalisable to the UK LHON population (please see Appendix D for further details on the validations).[6]

Table 1: Baseline characteristics from the weighted analysis

Parameter		Idebenone	SoC
Gender	Male, (%)	[redacted]	[redacted]
	Female, (%)	[redacted]	[redacted]
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		[redacted]	[redacted]
Time from first on set at baseline (months), mean		[redacted]	[redacted]
Baseline best visual improvement (LogMar), mean		[redacted]	[redacted]

Abbreviations: LogMAR – Logarithm of the minimum angle of resolution; 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, with an implicit imputation of missing values under a MAR assumption. As mentioned previously, the model was also run using a MNAR assumption, however, the company considers the missingness of the data to be MAR. Therefore, the MAR model was considered for the base-case. The MMRM analysis produced estimates for 6-month intervals from month 12 to month 48, using treatment group, analysis visit, treatment-by-analysis-visit interaction, gender, LHON mitochondrial DNA (mtDNA) mutation, time from onset at baseline, laterality at baseline, and best BCVA as fixed effects. The results of the analysis were supportive of the clear clinical benefit of idebenone over SoC.

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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 is presented in Table 2. A visual analysis of Table 2 is provided below, in

Figure 1.

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

Analysis visit	Estimated change in LogMAR ± SE (95% CI)		Estimated difference in LogMAR ± SE (95% CI)	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: CI – Confidence interval; LogMAR – Logarithm of the minimum angle of resolution; MMRM – Mixed models for repeated measure; SE – Standard error; SoC – Standard of care

Figure 1: Change in best BCVA in LogMAR derived from the integrated analysis as

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measured by a MMRM analysis

[redacted]

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

As demonstrated in Table 2 and

Figure 1:

- **At month 12**, there is an estimated mean worsening for SoC group with a LogMAR of [redacted] and a slight mean improvement of LogMAR [redacted] seen in the idebenone group. The difference between treatment groups is a LogMAR of [redacted], translating to a further improvement of ~[redacted] letters, which is statistically significant (p=<0.001) in favour of idebenone.
- Similar results are observed at **month 18**, with a difference between treatment groups of LogMAR [redacted], equivalent to ~[redacted] letters, which is statistically significant (p=<0.001) 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 (p=<0.001) in favour of idebenone with a difference of [redacted].
- At **month 36**, the estimated mean change vs baselines in SoC patients decreases slightly, likely due to the spontaneous recovery observed in some patients, and the difference between the treatment groups did not quite reach statistical significance ([redacted]). However, the difference is still in favour of idebenone with a difference of [redacted].

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. 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.

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The benefit demonstrated from the integrated analysis is also reflected in the economic model, where the estimated difference in change from baseline in LogMAR between the idebenone and SoC arm using the company's base-case transition probabilities derived from the logistic model under the MAR assumption provides similar estimates to those outputs from the integrated analysis. Please see the company's response to issue 3 for further details on the transition probabilities applied in the economic model.

This was further supported by UK clinicians who validated that the outputs from the company's economic model are comparable to the outcomes from the integrated analysis during the clinician validation interview conducted on October 17th, 2024. (Please see Appendix D for further details on the clinician validation).[6]

Achievement of 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 with at least one assessment on or after the 12-month analysis visit. For more detail on this please refer to the integrated analysis statistical report.[4]

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 3 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. The CRB trajectory was validated by UK clinicians during the clinician validation meeting conducted on October 17th, 2024, with one clinician noting the strength of the presented data. (Please see Appendix D for further detail on the clinician validation).[6]

Table 3: 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
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

Time to first CRR

In this integrated analysis, the variable of interest is time to first CRR (in months), defined as follows: (date of first CRR – date of baseline assessment +1) / 30.4375. Table 4 shows the time to first CRR for each treatment group based on a Kaplan-Meier (KM) analysis. The estimation of patients who met the definition of CRR responder increased with time for both treatment groups, but the proportion of patients who met the definition was consistently higher in the idebenone group, thus further supporting the efficacy of idebenone.

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Table 4: Time to first recovery in best BCVA

	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48
Idebenone							
At risk, weighted n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KM (SE), %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC							
At risk, weighted n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KM (SE), %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM – Kaplan-Meier; SE – Standard error; SoC – Standard of care

Figure 2 shows a KM analysis of the probability of attaining CRR, plotted against the time from baseline. The significant p-value for the weighted logrank test (p=[redacted]) shows that the idebenone group reached the first CRR faster than the SoC group.

Figure 2: Time to first recovery in best BCVA using KM analysis and weighted logrank test

Abbreviations: CRR – Clinically relevant recovery; SoC – Standard of care

Approaches explored to derive transition probabilities used in the economic model

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	Transition probabilities for both treatment arms were derived from the weighted analysis, produced from the integrated analysis set. For the period between 6 to 12 months from baseline, 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, multiple approaches have been applied. 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 stabilised inverse probability of treatment weights considering baseline variables of all ITT patients with at least one assessment at the month 12 analysis visit or after. The approaches used to estimate transition probabilities explored in the model include the following: 1. 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. The transition probabilities were estimated considering all merged imputed datasets under the MAR assumption, weighted by stabilised inverse probability of treatment weights. 3. The approaches under points 1 and 2 were repeated under the MNAR assumption. Please see the company's response to issue 3 for further details on the impact of each set of transition probabilities in the company's economic model. **<u>Conclusion</u>** In conclusion, the integrated analysis set uses all available clinical data to robustly inform the comparator data for the SoC arm and the relative treatment benefit of idebenone versus SoC. A MI approach was used to address concerns regarding missing data and further validate the efficacy outcomes of idebenone vs SoC. Furthermore, several approaches to modelling transition probabilities in both treatment arms in the economic model have been explored using the new integrated data which addresses any uncertainty in the robustness of the comparator data. The statistically significant relative treatment benefit has also been replicated within the economic model in order to ensure the value of idebenone is appropriately captured within the ICER. The integrated analysis has been used in the company's revised base-case as it provides the most complete and robust data with an accurate assessment of the value of idebenone in comparison to SoC to patients with LHON.
2: Model structure	**The company's original eight health state model structure best represents the natural disease progression of LHON and captures the true impact on patients. An integrated analysis and PS weighting analysis was performed using all available clinical data to address concerns on data imputation and demonstrated the robustness of the 8-health state model structure.** **<u>The company, EAG and committee's approach at ACM1</u>**

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	In the company base-case at ACM1, the economic model was a Markov state transition model that included 8 health states based on VA; LogMAR<0.3; LogMAR ≥0.3 and <0.6; LogMAR ≥0.6 and <1.0; LogMAR ≥1.0 and <1.3; LogMAR ≥1.3 and <1.7; counting fingers (CF); hand movement (HM) and light perception (LP). The EAG stated that the company's model structure was "*flawed because there was insufficient evidence to populate the transitions between the high number of health states in the model*". The EAG preferred a simplified model structure with 4 health states (limited visual impairment, moderate visual impairment, visually impaired [on-chart] and visual impaired [off-chart]). The committee also concluded that the high number of health states and limited observed transitions increased the uncertainty of the model structure, however, agreed that transitions between the worst health states with higher VA (CF, HM and LP) would be associated with significant benefit that would not be captured in a less sensitive model. The committee requested further analyses that show the sensitivity of the model to transitions. The company strongly considers the original model structure to be adequately robust and clinically and economically plausible for decision-making in patients with LHON. The 8 health states structure based on VA captures the natural progression of the disease over time. The structure has also been extensively validated by clinical experts in LHON and numerous other health technology assessment (HTA) bodies globally. The patient and clinical experts participating in ACM1 agreed that that company's modelled health states capture disease severity more comprehensively compared to the EAG's proposed model structure. Furthermore, the company's preferred structure is similar to model structures used in previous vision loss NICE technology appraisals (TAs). (TA274; diabetic macular oedema, TA283; visual impairment, TA298; choroidal neovascularisation).[7–9] **<u>The current model structure robustly captures the natural progression of LHON over time</u>** The 8 distinct health states based on VA were selected to capture the true clinical and economic burden of LHON. Even a small change in LogMAR ranges for each health state has a substantial difference in the daily functioning of patients with LHON which translates into quality-of-life (QoL) benefits and cost savings. ***Utility*** In Brown *et al.* (1999), utility values were derived based on VA levels with 0.1-0.2 LogMAR differences.[10] The study administered a visual function test consisting of 22 questions on basic activities for functioning in life, social issues, emotional or psychological issues, and activities of employment. Brown *et al.* (1999) reported that as each VA level decreased, the corresponding visual function test score also decreased across all levels, demonstrating the benefit of the extra granularity of the 8 health states included in the company's model structure. The greatest absolute decreases in total mean function test score occurred in between the VA levels corresponding to LogMAR 0.4 to LogMAR 0.6, LogMAR 0.6 to LogMAR 0.8 and CF to HM/LP. For example, there was a utility decrement of 0.17 between the CF and HM/LP health states reported, indicating it is highly inappropriate to group these health states together. In comparison, literature has demonstrated that the minimal clinically important difference, although in EQ-5D, can start from 0.07 in oncology, 0.04 in post-traumatic stress disorder and 0.03 in musculoskeletal diseases.[11] Combining these distinct LogMAR ranges together into single health states, as seen in the EAG's model structure, will not accurately capture the costs and effects modelled for patients with LHON and therefore will fail to robustly evaluate the cost-effectiveness of idebenone. Furthermore, a study by Lawrence et al (2023) provided utility values by health state for patients with LHON using 8 health state vignettes, which are aligned with the health states specified in the company's CEA.[12,13] The utility values from

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	Lawrence *et al.*(2023) also show an overall decrease in utility for each worsening of LogMAR health state which supports the results presented in Brown *et al.* (1999) and the assumptions used in the company's model. Please refer to response 6 and the updated CEA model for more detail on the utility values used in the company's base-case. ***Clinical and patient experts*** The need for 8 distinct health states is further supported by clinical and patient experts as part of ACM1 who stated that "*there are significant functional differences between being able to count fingers and just seeing hand movement*" and highlighted that these differences would not be captured by grouping all patients in the CF, HM and LP health states as off-chart. Patient experts also "*explained that being able to count fingers has practical implications for daily activities such as cooking, moving around the home and the ability to use devices. In contrast, relying only on hand movement perception severely limits independence and ability to perform daily activities*" (Section 3.10 DGC).[14] Therefore, it would be clinically inappropriate to group the off-chart health states together as the patient and clinical experts at ACM1 agreed that the company model structure captured the health states more comprehensively. **<u>The model structure has been extensively validated</u>** The original 8-state model structure has been subject to a comprehensive assessment carried out by other HTA bodies globally, including Scottish Medicines Consortium (SMC), All Wales Medicines Strategy Group (AWMSG) and National Centre for Pharmacoeconomics (NCPE) , and has been accepted each time.[15–17] Furthermore, the company's original model structure aligns with model structures demonstrated in TA274, TA283 and TA298, where up to 9 health states were defined by the Early Treatment Diabetic Retinopathy Study letter scale.[7–9] The economic analyses in these TAs were based on clinical data which consisted of a similar number of patients to this appraisal; TA298 and TA274 included only N=116 patients in the intervention arm. **<u>The EAGs proposed model structure presents a lack of distinction between VA levels</u>** The EAG's preferred model structure consists of four health states based on VA; Limited visual acuities (LogMAR<0.3); Moderate visual acuities (LogMAR ≥0.3 and LogMAR <1.0); On-chart visually impaired (LogMAR ≥1.0 and LogMAR <1.7); Off-chart visually impaired (CF-LP). Whilst the EAG disagreed with the high number of health states used in the company's original model structure, the EAGs preferred model structure presents an unreasonably simplified interpretation of such a complex and debilitating disease such as LHON, underestimating the cost-effectiveness of idebenone in LHON. Whilst the EAG adapted the model structure to align more with the structure used in highly specialised technologies (HST) 11, there are substantial differences in the modelled population and distribution of health states in HST 11 compared to this appraisal. HST 11 primarily models patients who are classified as legally blind (LogMAR > 1) and health states for patients with VA of LogMAR < 1 were not included. As a result, the health states included in the economic analysis of HST 11 are still only defined by small LogMAR ranges. For example, in HST 11, 'HS2' is defined as 1.0 ≤ LogMAR < 1.4 and 'HS3' is defined as 1.4 ≤ LogMAR <1.8. However, in the EAG's proposed health states for this appraisal, patients would be grouped based on large varying LogMAR values ('Moderate visual activities' [MVA]: 0.3 ≤ LogMAR ≤ 1.0; 'On-chart visual activities' [OnVA]: 1.0 < LogMAR ≤ 1.7).

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	Furthermore, HST 11 states that due to few recorded observations in the NH data that were used, the HM, LP and NLP (no light perception) states were grouped together into one health state, 'HS5'. In HST 11, only 3% of patients were in this grouped health state at baseline. In comparison, in the company model, an average of [redacted]% of patients (n=[redacted]) from the integrated analysis conducted make up the EAG's proposed combined health state of 'Off-chart visual acuities' (OffVA), consisting of CF, HM and LP, which is a substantial proportion of the model population with varying levels of VA. The inappropriateness of grouping together the CF, HM and LP health states is further supported by patient and clinical experts and the NICE committee. As highlighted above, the DGC states that the "*patient and clinical experts disagreed with the EAG's health states, particularly the lack of distinction between health states with lower VA*". The committee also noted that "*transitions between CF and states with higher VA would be associated with a significant benefit that would not be captured in a less sensitive model*". (Section 3.10, DGC[14]) The 8-state model structure was further validated by all clinicians during the clinician validation interview conducted on October 17th, 2024, who unanimously stated that the split of the off-chart categories (CF, HM and LP) is highly appropriate to accurately capture the impact of LHON on patients with lower VA. There was also consensus among the clinicians that the on-chart categories provided sufficient granularity and aligned with previous NICE health TAs. (Please see Appendix D for further details on the clinician validation).[6] The company considers the original, eight health state, model structure to accurately capture the natural disease progression of LHON as supported by the measure of health-related quality-of-life (HRQoL) between VA levels, clinical and patient experts and numerous other HTA bodies. To provide a robust and accurate clinical and economic evaluation of idebenone it is not considered clinically appropriate to group together defining health states such as CF, HM and LP. **<u>The integrated analysis provides sufficient data for 8-health states</u>** Table 5 presents an overview of the frequencies of BCVA assessment by analysis visits in the idebenone arm included in the integrated analysis. From this table, it can be observed that the number of assessments from idebenone patients contributing to the integrated analysis is 250 at month 24. In comparison, only 16 patient counts (including imputed values) were included from the EAP data alone for the month 21 to month 24 cycle in the company's previous base-case. The drop in assessments from month 24 to month 30 in Table 5**Error! Reference source not found.** is likely due to the ending of the LEROS studies. Additionally, the integrated analysis set also incorporates all available clinical data for modelling the SoC arm, with further details discussed in issue 4 of this document. Similar to the idebenone arm, there is an increase in assessments contributing to the SoC arm (Table 7) and the company's response to issue 4 of this document demonstrates how the use of the integrated analysis set overcomes the EAG and committee's concerns around the low number of observations to inform the SoC transition probabilities. Therefore, the company is confident that the use of the integrated analysis set, and transition probabilities derived from the integrated analysis overcomes the issues presented by the EAG and committee. The use of the integrated analysis allows for sufficient observations to inform transitions between all 8 health states, which eliminates

the need for data imputations and a LOCF approach as the logistic model estimates inputs for every health state. Therefore, the updated transition probabilities derived from the integrated analysis provide an accurate and robust approach to modelling the use of idebenone and SoC for LHON patients in an 8-health state model.

Table 5: Frequencies of BCVA Assessment by Analysis Visits - idebenone arm

Analysis Visit (N)				
Visit (month)	**Frequency**	**Percent**	**Cumulative Frequency**	**Cumulative Percent**
6	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]	[redacted]
48+	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA – Best corrected visual acuity

However, to address the committee's request for "*further analyses that show the sensitivity of the model to transitions*", the company has tested both the company's original 8-state model structure and the EAG's preferred 4-state model structure, through several alternative transition probability scenarios. These transition probabilities were derived from the integrated analysis conducted pooling all data sets (see points 1-3 in response 1 and the SAP for more detail), This analysis produced multiple sets of transition probabilities for:

- A logistic regression model for MAR and MNAR datasets
- A weighted observed for MAR and NMAR datasets

Table 13 and Table 14 presents the scenario analysis results from the alternative transition probabilities explored using both the company's original 8-state model structure and the EAG's preferred 4-state model structure respectively. The results from these scenarios show that the ICER varies from £24,894 to £28,735 using the company's original 8-state model structure, and £28,345 to £32,627 using the EAG's preferred 4-state model structure under the company's revised base-case. These scenarios provide reassurances that the company's original 8-state model structure is sufficiently robust to variations in transition probabilities and provide similar outputs to the EAG's preferred 4-state structure.

In conclusion, given the range of scenarios the company has explored, including four new sets of transition probabilities based on integrated analyses, the revised company base-case uses the company's original 8-state model structure because it robustly captures natural progression of LHON over time, as supported by the measure of HRQoL between VA levels, clinical and patient experts and numerous other HTA bodies. In addition, further analysis has shown it to be sufficiently robust to variations in transition probabilities as explored in scenario analyses. The revised company base-case ICER is £28,451 (Table 10).

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	Given the importance of ensuring the impact of visual impairment on patients and the natural progression of LHON has been accurately captured within proposed health states and therefore the measure of HRQoL and resource use within this CEA, the company remains confident that this model structure is the most suitable structure for providing an accurate and fair cost-effectiveness evaluation of idebenone whilst addressing the uncertainties highlighted by the EAG and the committee.
3: Modelling idebenone long-term treatment effect	**The long-term treatment effect of idebenone is based on the outcomes from the integrated analysis set, which uses all clinical data from 12 months onwards. These data are used to ensure the long-term treatment effect of idebenone is based on the most available observations to ensure the long-term treatment effect is robustly modelled in the economic model.** **<u>The company, EAG and committee's approach at ACM1</u>** The data collected within the RHODOS RCT were used to inform the transition probabilities in the idebenone arm from baseline to month 6 in the CEA in the company's original base-case. However, as the 24-week duration of RHODOS was not long enough to demonstrate the full benefit that idebenone has on patients with LHON, further data were needed to supplement the clinical effectiveness of idebenone in the long-term. The baseline characteristics, specifically the mutations and gender, of patients in the LEROS and RHODOS study were not considered to be comparable. Therefore, it was considered appropriate to exclude LEROS data from the economic model due to the heterogeneity between the patient populations and its lack of generalisability to patients in UK clinical practice. Instead, the company used real-world evidence (RWE) in the form of the EAP study to supplement the data from RHODOS and inform the transition counts of the idebenone arm in the long-term. Baseline characteristics of idebenone-treated patients in the EAP and RHODOS studies were broadly similar in terms of age, gender, VA severity and mutation type. The RHODOS and EAP studies were considered sufficiently similar in terms of population, analysis methods and outcomes which supports the use of EAP to determine idebenone transition probabilities after six months. Therefore, the EAP data were used to supplement the RHODOS data to inform the effectiveness of idebenone in the long-term (post 6 months). The use of the EAP data allows for longer follow-up of data to be incorporated into the CEA as the duration of the EAP study is 36 months compared to the 24-month duration of LEROS. The company considers that this longer-term data reduces the uncertainty in a rare disease where available data are already limited. This aligns with UK clinicians who confirmed that VA would be expected to remain stable after 3 years of treatment during the first clinician interviews conducted in August 2023. (Please see Appendix N for further details on the clinician validation).[18] The EAG had concerns over the company's choice of the EAP as the preferred source of long-term effectiveness in the economic model as, despite the overall length of follow-up for the EAP being longer, the availability of data were considerably lower. The EAG considers that the LEROS study is more appropriate to inform the idebenone treatment effect after RHODOS, and as such, the company was requested at the clarification stage to conduct a scenario deriving idebenone transition probabilities using the LEROS ITT population. The company complied with the EAG's request, with the base-case ICER at ACM1 increasing from £18,578 to £21,129 in the scenario. **<u>The use of the integrated analysis to inform idebenone long-term treatment effects</u>**

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	To overcome the issues presented by the EAG in their report, the company produced an integrated analysis set, as detailed in response 1. This integrated analysis uses all available clinical data for modelling the idebenone arm, including the EAP and LEROS studies. Using the integrated analysis, transition probabilities have been derived using PS weights and a MI approach and are now used to inform the company's base-case CEA. In the CEA base-case, transition probabilities post-month 12 are estimated using a logistic regression model and a MAR assumption. When exploring the alternative transition probability approaches in the company's economic model, the outputs are all similar to the outputs of the integrated analysis, as demonstrated in Table 6 below. The difference in mean change from baseline of LogMAR between idebenone and SoC from the integrated analysis is [redacted] at month 12. This is compared to a difference of LogMAR [redacted] across the different transition probability scenarios from the economic model. Given the approaches explored to derive the transition probabilities as detailed under points 1-3 in response 1 (page 12), the company has adopted the following approaches for informing transition probabilities in the updated base-case: • **Baseline – month 6:** Transition probabilities from baseline to month 6 are derived directly from data collected as part of the RHODOS RCT (as previously modelled). • **Month 6 – month 12**: Transition probabilities are derived from the integrated analysis 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 MAR assumption as detailed under point 1 in response 1. • **Month 36 onwards**: As a conservative assumption: 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. Therefore, a conservative approach was adopted, assuming no further improvement, where patients are assumed to accrue costs and QALYs in the health state they end in at month 36 for the time horizon of the model. For the transition probabilities derived from the integrated analysis and used in the company's base-case in the idebenone and SoC arms, please see Table 16 of Appendix B. For more details on the derivation of the transition probabilities, please refer to the SAP. In addition to the company's health states, the transition probabilities were also run using the EAG's preferred 4- health state model. To address any uncertainty in the transition probabilities chosen to inform months 12 to 36 in the economic model, several scenarios have been explored using the alternative analysis sets detailed under points 1-3 (page 12) in response 1: 1. **Month 12 – month 36**: PS weighted, MI, logistic model, MNAR analysis (as detailed under point 1 in response 1) 2. **Month 12 – month 36**: PS weighted, MI, weighted observed MAR analysis (as detailed in point 2 under response 1)

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3. **Month 12 – month 36**: PS weighted, MI, weighted observed MNAR analysis (as detailed in point 3 under response 1)

The difference in the mean change from baseline of best BCVA for idebenone vs SoC outputted from the model is presented in the table below (Table 6). As demonstrated, the outputs of the economic model using the various transition probabilities are all similar to the clinical outputs demonstrated from the integrated analysis set.

Table 6: Difference in mean change in best BCVA idebenone vs SoC

Analysis visit	Difference in mean change in best BCVA idebenone vs SoC from the economic model (LogMAR)* P-value				Difference in mean change in best BCVA idebenone vs SoC from the integrated analysis (LogMAR)
	Logistic model, MAR	Logistic model, MNAR	Weighted observed, MAR	Weighted observed, MNAR	
Baseline	0	0	0	0	-
Month 3	[redacted]	[redacted]	[redacted]	[redacted]	-
Month 6	[redacted]	[redacted]	[redacted]	[redacted]	-
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA – best corrected visual acuity; MAR -missing at random; MNAR – missing not at random; 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 6), the company presented the difference in the mean change in BCVA of idebenone vs SoC as derived from the integrated analysis alongside the outputs from the economic model using the several transition probabilities approaches to clinicians during a clinician validation interview conducted on the 17th of October 2024 (please see Appendix D for further details on the validations).[6] Both of the clinicians interviewed agreed that the outputs from the company's economic model are comparable to the outcomes from the integrated analysis (lease see Appendix D: Clinician validation interview for further details)[6]

As demonstrated in Table 6, the four approaches at deriving transition probabilities provide extremely similar outputs at each timepoint, demonstrating the robustness of each method used. Furthermore, the different transition probability approaches also create similar ICERs in the company's updated base-case ranging from £24,894 to £28,735. These scenarios were also run using the EAG's preferred model structure and the scenario ICERs are demonstrated in Table 14.

Table 5, in response 2 of this document presents an overview of the frequencies of BCVA assessment by analysis visits in the idebenone arm. The number of assessments falls to [redacted] after month 36 which is a natural limitation to the clinical data. Due to this limitation, the company only model transition probabilities up until month 36. As part of the clinician

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	validation process on October 17th, 2024, the company validated the assumption that patients do not transition health states from month 36 onwards. The clinicians highlighted they would still expect to see patients move health states after month 36, however, given the limitations in the data past month 36 and the strength of the integrated analysis up to 36 months, all clinicians agreed that it is appropriate to assume movement up to that point. (Please refer to Appendix D for more details on the clinician validation).[6] The company is confident that the use of the integrated analysis set and transition probabilities derived from the integrated analysis overcomes the issues presented by the EAG regarding the low patient numbers in the EAP dataset and provides an accurate and robust approach to modelling the long-term treatment effect of idebenone. **Change in LogMAR from baseline** To ensure the data outputs from the integrated analysis set are in line with clinical expectations, the company presented the estimated difference in change in LogMAR from baseline from the integrated analysis to clinicians (presented in Table 2, response 1). The change in the difference in LogMAR between idebenone and SoC is statistically significant up to month 36. Specifically, the difference between treatments favoured idebenone vs SoC with a mean reduction in LogMAR of [redacted] at 12 months, and [redacted] at 30 months. During the clinician validation interview conducted on 17th October 2024, both clinicians confirmed that the trajectory presented in Table 2 is representative of clinical practice. One clinician commented that the data are realistic as *"what seemed like spontaneous recovery was captured in the results of the analysis at month 36 and the difference in the mean change of LogMAR from baseline between idebenone and SoC was no longer statistically significant."* (Please refer to Appendix D for more details on the clinician validation).[6] To conclude, the use of the integrated analysis set and weighted analysis to inform the modelling of the long-term treatment effect of idebenone ensures all available data are used within the CEA and allows the value of idebenone to be accurately reflected. The weighting conducted in the integrated analysis also addresses the EAG's concerns of differing time since symptom onsets across studies.
4: Modelling SoC long-term treatment effect	**The use of the integrated analysis and weighted analysis incorporates all available clinical data providing the most complete and robust data to inform the long-term SoC treatment effect. In addition, the integrated analysis addresses the uncertainty around the limited number of observations informing the transition probabilities in the long-term.** **The company, EAG and committee's approach at ACM1** The data collected within the RHODOS RCT was used to inform the transition probabilities in the SoC arm from baseline to month 6 in the CEA in the company's original base-case. For month 6 up to month 36 the SoC transition probabilities were then derived from CaRS-I which was used to inform the long-term effect of SoC. This was the only data available to the company at the time of submission for SoC patients. Due to the ultra-rare nature of LHON, available data on the natural progression of patients receiving SoC in literature is substantially limited. Therefore, the company considered the best available data, which was the real-world data (CaRS), to inform the long-term SoC arm that was used at the time of submission. The suitability of using the CaRS-I data in the company submission to determine how placebo patients from the RHODOS study may transition between LogMAR VA health states after six months was evaluated. From this, it was concluded that baseline characteristics of placebo-treated patients in the CaRS-I and RHODOS studies were similar in terms of age, gender and mutation type. To overcome the variable follow-up time in the CaRS-I dataset a windowing approach was used to classify CaRS-I patients into

three-monthly visits. Hence, despite some heterogeneity in terms of the population and analysis methods, the similarity in outcomes confirmed the suitability of using CaRS data for determining transitions post-six months.

The EAG was critical of the company's use of the observational CaRS-I study alone to inform the long-term SoC treatment effects due to the low number of observations. As part of the company's response to the clarification question B21, the company provided a scenario using pooled CaRS-I and CaRS-II data with no observation carried forward using the EAG preferred health states to model the SoC arm which demonstrated an ICER of £12,295.

The use of the integrated analysis to inform long-term SoC treatment effect

To overcome the issues presented by the EAG in their report, the company has produced an integrated analysis set, as detailed in response 1. The integrated analysis set incorporates all available clinical data for modelling the SoC arm. Using the integrated analysis, transition probabilities have been derived using PS weights and a MI approach and are now used to inform the company's base-case CEA.

In the CEA base-case, transition probabilities post-month 12 are estimated using a logistic regression model and a MAR assumption. Three alternative scenarios were run as described in response 3 (page 18) with methods detailed in response 1 (page 12). For more details on the derivation of the transition probabilities and the impact in the economic model, please refer to the company's response to issue 1 and issue 3 of this document and the SAP.

Table 7 presents an overview of the frequencies of BCVA assessment by analysis visits in the SoC arm. From this table, it can be observed that the number of assessments from SoC patients contributing the integrated analysis is [redacted] at month 24. In comparison, without the LOCF assumption, patient counts were mostly imputed for the SoC arm at the month 21 to month 24 cycle in the company's previous base-case.

This increase in observations demonstrates how the use of the integrated analysis set overcomes the EAG and committee's concerns around the low number of observations to inform the SoC transition probabilities. Furthermore, due to the transition probabilities being informed and derived using the propensity weighted, logistic model, there is no longer a need to use a LOCF approach to inform probabilities in the SoC arm of the CEA. The company is confident that the use of the integrated analysis set overcomes the issues presented by the EAG regarding the low patient numbers in the CaRS-I dataset.

Table 7: Frequencies of BCVA Assessment by Analysis Visits - SoC arm

Analysis Visit (N)				
AVISITN	**Frequency**	**Percent**	**Cumulative Frequency**	**Cumulative Percent**
6	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]

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	<table><tr><td>**36**</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>**42**</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>**48+**</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table> Abbreviation: BCVA – Best corrected visual acuity, SoC – Standard of care To conclude, the use of the integrated analysis set and weighted analysis to inform the modelling of the long-term treatment effect of SoC ensures all available data are used within the CEA and creates an accurate representation of how VA changes for patients receiving SoC over time. The company is confident that the introduction of the integrated analysis and weighted analysis creates the most robust estimates of the transition probabilities to inform the long-term treatment effect of SoC.
5: 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 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 clinical experts would expect to see in clinical practice.** **<u>Company base-case and EAG preferences</u>** In the company base-case at ACM1, idebenone treatment duration was informed using the KM estimates of pooled persistence data from the RHODOS and the EAP studies for up to month 36, after which it was assumed that all patients would discontinue treatment. This treatment duration was aligned with the length of follow-up data provided from the EAP study for the transition probabilities. The EAG preferred to use the RHODOS/EAP persistence data as a source to inform time on treatment up to month 36 whilst using the RHODOS/LEROS data to inform transition probabilities for up to month 24. The NICE 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*" (Section 3.13, DGC[14]). Clinical experts stated that *"in clinical practice, they would use idebenone for up to 2 years if LHON is responding or until LHON stabilisation*" (Section 3.13, DGC[14]; company submission (CS), Appendix N[18]). The committee concluded "*that 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)*." (Section 3.13, DGC[14]) **<u>Mechanism of action</u>** As stated in the company submission, according to the biochemical mode of action, idebenone is thought to re-activate viable but inactive RGCs in LHON patients by restoring cellular energy (ATP) generation [19]. Depending on the time since symptom onset and the proportion of retinal ganglion cells (RGCs) already affected, idebenone can promote recovery of vision in patients who experience vision loss [19]. Once patients have stabilised and stopped treatment they are not expected to go back on treatment, and there is no evidence of treatment waning. The RHODOS-OFU data demonstrates that: "*The difference between idebenone and placebo remained stable confirming the maintenance of treatment benefit of idebenone after 24 weeks of treatment beyond 2.5 years without therapy*", even with idebenone treatment only lasting for six months. (CQ: B7b[20]). So, patients should take idebenone until stabilisation, indicating that all inactive but viable RGCs have been activated.

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	The company considers it to be the most clinically plausible for patients to be treated until stabilisation. This was confirmed in interviews with clinical experts who said that: "*in patients who show a CRR to idebenone, treatment should be continued until there is a stabilisation, or 'plateau' of VA*.", which according to one of the clinicians would be characterised by two consecutive visits with no change in VA. (CS; Appendix N: Clinical validation[18]) **EAP trial design** The company wishes to reiterate that exposure to idebenone in the EAP is not reflective of how idebenone would be used in clinical practice. The EAP study is of a retrospective, non-controlled and open-label nature. Furthermore, at the time of the onset of the EAP, the required treatment duration was poorly understood. Therefore, within the EAP study, there is a non-uniform duration of treatment and a deliberately broad range of treatment duration, of up to five years, was permitted. This leads to varying lengths of treatment durations within the EAP study; treatment duration for the efficacy population in the EAP study ranged from 2.4 to 70.4 months. For this reason, the company thinks that this study should not be used to justify treatment duration beyond three years. The company also finds it unlikely that patients will be on treatment for longer than three years. This has been confirmed by expert opinion to the company prior to the NICE submission, which suggests that it would be unlikely that there would be a need to treat beyond 3 years except in very rare cases. **Treatment duration as part of the integrated analysis** As part of the integrated analysis, the length of time patients should receive treatment was explored. There is great variability in the treatment duration across the multiple LHON studies; in LEROS, patients are treated for 24 months, whereas in the EAP, an RWE study, some patients remained on treatment for over 5 years. Given the variability, the company explored an analysis looking at the time to *indication* to treatment discontinuation using the integrated analysis dataset. As highlighted by clinicians in the pre-submission clinician validation (CS; Appendix N: Clinical validation[18]), and during discussions as part of this response to the DGC, patients are expected to be treated with idebenone until stabilisation or a 'plateau' of VA. Clinicians highlighted that this is often around 2-3 years after the start of treatment with idebenone. Therefore, KM estimates were derived for the 'time to indication of treatment discontinuation' considering the following patients as eligible to be discontinued from treatment: • 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. The KM curve estimating the proportion of patients who should discontinue treatment based on clinician input is presented in Figure 3 and informs the treatment calculations in the company's economic model.

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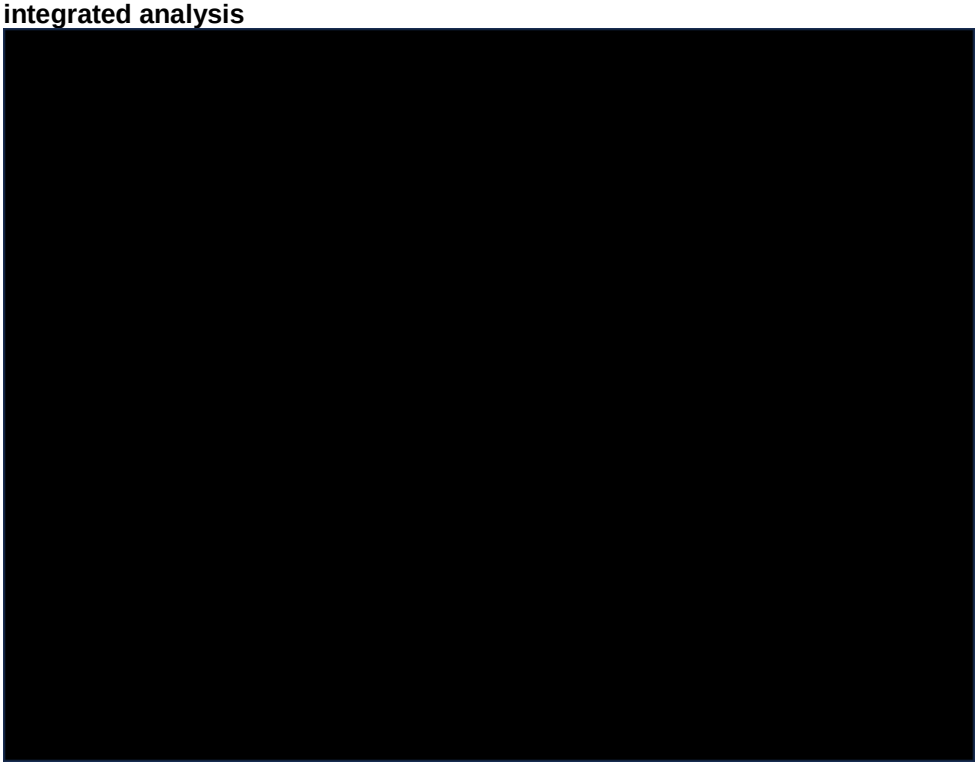
Figure 3: Time to indication to treatment discontinuation estimated using the integrated analysis



As demonstrated in the KM curve above 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. However, the company would like to highlight that there is only one patient at risk from month 36 onwards making the estimates past this timepoint very uncertain. The KM estimates presented in Figure 3 were also shared as part of the company clinician validation (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.[6]

Furthermore, the length of treatment derived from the analysis presented above aligns with the length of time that patients can transition across health states in the model (month 36).

Updates to the company base-case

As described in the company's response to issue 1, the company has now updated their base-case with data from the integrated analysis to inform the modelling of clinical effectiveness in the CEA. Therefore, for alignment, the modelling of treatment duration within the CEA is now informed using the time to indication to treatment discontinuation KM estimates presented in Figure 3. For the company's updated base-case ICER, please see Table 10.

To conclude, given the importance of ensuring the time on treatment seen in clinical practice is accurately reflected in the CEA and aligns with the data source used to inform

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	the clinical effectiveness, the company is confident that time to indication to treatment discontinuation KM estimates from the integrated analysis is the most appropriate source to inform treatment duration for patients receiving idebenone.
6: Patient HRQoL	***Lawrence et al. (2023) is the most appropriate source for measuring patient HRQoL as the study uses the HUI-3 to estimate utilities for different levels of vision loss in LHON patients. The HUI-3 HRQoL measure is preferred to the EQ-5D-5L as the HUI-3 can capture the impact of different levels of visual impairment, which the EQ-5D is not sensitive enough to detect.*** In the company base-case at ACM1, patient HRQoL was estimated using the utility values from Brown *et al.* (1999), a TTO study evaluating utility values of the better-seeing eye in 325 patients with visual impairment across 'on-chart' and 'off-chart' visual acuities. The EAG preferred to use the utility values measured by EQ-5D-5L as presented in the Lawrence *et al.* (2023) study. The committee also concluded that Lawrence *et al.* (2023) was a more appropriate source to derive utility values from, however, stated in the DGC that "*the source of utility values had a minimal effect on the cost-effectiveness results in the EAG's base-case*" and "*it would like to see further scenarios explored using varying utility values, in particular, for reflecting a CF health state*".(Section 3.14, DGC[14]) The company recognises that NICE's preferred measure of HRQoL in adults is the EQ-5D, however, as previously stated in the company submission, EQ-5D is highly inappropriate for measuring HRQoL in eye conditions. NICE guidelines (DSU TSD 8)[21] state that "*evidence from recent reviews suggests that EQ-5D is probably not appropriate for assessing the impact of some specific forms of visual impairment*" and suggest alternative preference-based measures instead. Furthermore, literature has already shown that EQ-5D has poor convergence validity when used in visual disorders and that the EQ-5D index shows poor performance at detecting vision impairment.[21,22] This is further supported by the use of alternative measures of HRQoL which were implemented in numerous other similar HTAs in eye conditions, including HST 11 (TTO), TA 298 (TTO), TA 274 (NICE preferred TTO), TA 283 (TTO) and TA 294 (EAG preferred TTO in better-seeing eye model).[7–9,23,24] The utility source used by the company as part of the TA and the EAG/ NICE preferences for each of these TA submissions are summarised in Table 8. As seen in Table 8, for each of the TAs, the EAG/ NICE preferred a TTO-based utility source over an EQ-5D utility source, further demonstrating that EQ-5D values are inappropriate to be used as a utility source for patients with visual impairments. While several TAs presented in Table 8 have an expressed NICE/ EAG preference for TTO-based utilities sourced from Czoski-Murray et al. (2009) this publication provides one utility value for all patients with logMAR of 1.3 or more.[25] As previously stated in response 2, the company strongly believe patients in worse health states should be modelled separately and therefore the HUI-3 utility values reported by Lawrence et al. (2023) are the most appropriate. Additionally, considering the time elapsed since the Czoski-Murray study was published in 2009, which is now outdated, our analysis has leveraged more contemporary research by Lawrence *et al.* (2023). This newer publication enables us to incorporate the most recent data and knowledge into our utility value assessments, thereby ensuring alignment with current evidence-based standards. **Table 8: Utility measures used in previous NICE TAs** **NICE TA** | **Utility measure adopted by the company** | **Utility measure preferred by EAG/ committee**

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HST11	**Base case:** HUI-3 utility values collected from the company's elicitation exercise (Lloyd et al. [2019]) To derive the utility values six retina specialists were interviewed to provide a proxy valuation of each vignette using the HUI3 questionnaires.[23]	**EAG preference:** TTO utility values derived from Rentz et al. (2014).[26] Rentz et al. (2014) was a general public TTO study that looked at 8 health states with varying degrees of vision problems defined by 6 items of a disease-specific HRQoL questionnaire (NEI VFQ-25).[26]
TA298	**Base-case**: TTO utility values reported in Czoski-Murray et al. (2009).[25]	**EAG preference:** TTO utility values derived from Brown et al. (1999).[10]
TA274	**Base case:** EQ-5D collected from the clinical studies. EQ-5D data from RESTORE were transformed to utility values using standard social tariffs and then related to visual acuity in the treated eye using linear regression.	**Committee preference:** TTO utility values reported in Czoski-Murray et al. (2009).[25]
TA283	**Base case:** TTO utility values reported in Czoski-Murray et al. 2009.[25] Utility values were derived by applying a regression equation from the Czoski-Murray et al. (2009) publication to derive utilities for each of the 8 BCVA health states.[25]	**EAG preference:** TTO utility values reported in Czoski-Murray et al. (2009).[25]
TA294	**Base case:** EQ-5D data from clinical studies. EQ-5D data from VIEW 2 were transformed into utility values using the UK population tariff.	**EAG preference:** TTO utility values derived from Brown et al. (1999).[10] The EAG preferred the values from Brown et al. (1999) when modelling the better-seeing eye.

Abbreviations: EAG – external assessment group; HST – highly specialised treatment; TA – technology assessment; TTO – time-trade off.

The company base-case at ACM1 utilised the utility values derived from Brown *et al.* (1999), as this is a TTO study, which is aligned with the NICE and EAG preference in TAs in other eye conditions. Additionally, values are based on the better-seeing eye which aligns with the company's original model structure of this CEA.[10] The better-seeing eye also has a higher predictability and consistency when measuring QoL compared to the worst-seeing eye. This principle was supported in the appraisal for aflibercept for treating wet age-related macular degeneration (TA294),[24] where the EAG suggested that Brown *et al.* was a more suited source than EQ-5D data for measuring HRQoL in the better-seeing eye model. Although the EAG stated that Brown *et al.*(1999) "*had a higher age than people with LHON*" (67.5 years), the age range of the study population started from 28 years of age, which is lower than the mean age of patients included in this CEA (34 years).

The company acknowledges that Lawrence *et al.* (2023) is the only study that provides utility values specifically based on LHON. The study describes the development of eight

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	health state vignettes which varied by level of VA, defined by LogMAR score, similar to the company's original model structure health states at ACM1. However, the EQ-5D-5L data within the study demonstrated some 'misordering' of health states, where a 'better' health state had a lower utility value than a 'worse' health state (LogMAR 1.0 – 1.3: 0.495; LogMAR 1.3 – 1.7: 0.497 [in the combined UK and ROI population]), which further supports the rationale that EQ-5D is not appropriate for detecting visual impairment.[12] However, the company recognises the value of using LHON-specific utility values for this CEA. To address the concerns of using the Brown *et al.* (1999) utility values, the company, proposes the use of HUI-3 derived utility values from Lawrence *et al.* (2023) in the updated base-case CEA. As the HUI-3 values are also derived by Lawrence *et al.* (2023), they are similarly collected from a UK and ROI population with an average age of 46.5 years. This addresses the EAG's concerns of mean age being not reflective of the mean age of patients with LHON, and the lack of UK data that was highlighted in the company's choice of Brown *et al.* (1999). Using HUI-3 in the updated company base-case also aligns with the committee's conclusion that Lawrence *et al.* (2023) is a more appropriate source to derive utility values (Section 3.14 DGC[14]). Additionally, the company considers the HUI-3 valuation more appropriate than the EQ-5D as the HUI-3 includes questions specifically related to vision, capturing the true burden of visual impairment associated with LHON. Furthermore, the HUI-3 results in the Lawrence *et al.* (2023) study showed the most reflective level of difference by VA which is supported by clinical and patient experts statement as part of the ACM1 that "*there are significant functional differences between being able to count fingers and just seeing hand movement*" and also by Longworth *et al.* which stated that *"HUI-3 is able to capture HRQoL for vision impairment*".[22] Furthermore, in a study comparing health state valuations (HUI-3, EQ-5D, EQ-VAS, and TTO) in patients with diabetic retinopathy it was found that the HUI-3 detected significant differences between patient groups classified according to visual impairment in the worse eye. Additionally, HUI-3 recorded a difference of 0.43 in health state values between normal vision and blindness in the better eye, which is more than twice that captured by the other measures (EQ-5D, EQ-VAS and TTO; 0.15-0.20), as well as showing the highest and statistically significant correlation with NEI VFQ-25.[27] Therefore, the company strongly considers the use of the HUI-3 utility values reported in Lawrence *et al.* to be the most suitable alternative measure for HRQoL within this CEA, as the HUI-3 valuation specifically accounts for QoL associated with visual impairment, something the EQ-5D questionnaire does not. Furthermore, the HUI-3 utility values from Lawrence *et al.* (2023) are still derived from a LHON-specific study with a UK and ROI population. During the most recent clinician interview, one clinician also highlighted that HUI-3 seemed to be most helpful in measuring utility values due to the vision component (17th October 2024, Appendix D).[6] The company has revised the company base-case to use the HUI-3 values reported in the study by Lawrence *et al.,* as these are able to capture the QoL associated with visual impairment as well as being based on a UK and ROI population. The revised company base-case ICER is £28,451 (Table 10). To address the committee's request for "*further scenarios explored using varying utility values",* the company has run several scenarios using several utility sources explored including the following utility sources: Lawrence et al 2023 (EQ-5D-5L and TTO), Brown et al (1999), Czoski-Murray (2009), and Rentz *et al.* (2014) . All scenarios run by the

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	company and their respective ICERs these sources produce in the model can be found in Table 13. In conclusion, the revised company base-case has been updated to model the patient HRQoL based on the HUI-3 values reported in the study by Lawrence *et al.* Given the importance of ensuring the impact of visual impairment on patients has been accurately captured within the utility values and measure of HRQoL within this CEA, the company remains confident that these utility values are the most suitable utility values for measuring QoL within patients with LHON.
7: Caregiver HRQoL	**To accurately capture the burden of LHON and the value of idebenone, it is important to include a caregiver disutility in the base-case CEA as the impact of caring for a patient with LHON poses a substantial QoL burden to caregivers.** The company base-case at ACM1 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.[23,28] 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.[29] 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). Given that quantitative caregiver QoL was not collected in the clinical trials for idebenone and the literature on the disutility of caregivers of patients with LHON and other ophthalmological diseases is limited, the company considered it appropriate to use the caregiver disutility values from Wittenberg *et al.* (2013), as aligned with HST 11 for patients with a LogMAR of 1.0 or more. However, in the DGC report, the EAG stated that the HST 11 appraisal "*considered 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."*. (Section 5.15, DGC[14]) The company would like to highlight that in the HST 11 appraisal, the caregiver disutility is applied to all patients in the base-case, not only children. The EAG of HST 11 agreed with this approach and included it in their base-case. Furthermore, the EAG of HST 11 also preferred to apply the caregiver disutility to all modelled health states in the CEA of HST 11, all of which cover a LogMAR>1 VA. Therefore, it is not appropriate to use HST 11 as a justification for assuming that a caregiver disutility should not be applied to adults in this CEA. In the ACM1 meeting, the EAG suggested that excluding values for caregivers of adults was appropriate as adults would be more accustomed to vision loss and thus require less support compared to children with LHON. However, the company strongly disagrees with this approach as LHON is a severely debilitating condition characterised by a rapid vision loss in adulthood (LHON patients experience very rapid vision loss of VA with over 50% of eyes deteriorating to LogMAR above 1.0 within one week of disease onset) and therefore, caregiver support is essential.[30] Support in the form of informal care from family members and other caregivers is absolutely fundamental to patients with LHON, particularly in the beginning stages of their vision loss whilst the patients are adjusting to the substantial life change of losing their vision. Additionally, LHON typically occurs in the second and third decades of life[31], at a time when patients are expected to be beginning their careers or starting a family. This suggests that patients with LHON will require a substantial amount of support from caregivers to adjust to an unknown way of living. This is further supported

	by the EAG's clinical experts which "*explained that most people with LHON need constant support from family members and carers*" (Section 3.15, DGC[14]). Therefore, the company considers it imperative to include caregiver disutility in the base-case CEA to accurately reflect the impact LHON has on caregiver QoL for adult patients undergoing a substantially challenging change in their daily living. **<u>The impact on caregiver QoL as demonstrated in literature</u>** The impact of caring for an individual with LHON on caregiver QoL is also demonstrated in literature. The QoL burden to caregivers of patients with LHON is demonstrated in the study by Williams *et al.* (2023). [32] The study included N=9 caregivers and family members who cared for adult patients with LHON, with mean age of 32 years old (range: 17-73 years old). The study suggests a substantial burden for many caregivers with impacts reported across numerous aspects of life; emotional, daily life, social life and relationships, work and career, financial and wider family. The study reports that caregivers "*discussed how their daily routine and activities had changed to accommodate their care tasks*" and "*worry about the future was a prominent theme across interviews*". The study also reports a substantial emotional burden and that "*Mothers discussed immense feelings of guilt for passing on a gene that caused their child's vision loss*" and the "*profound emotional impact of caring for someone with LHON had knock on effects on other areas of life*". Furthermore, a recently published poster by Ahmadu *et al.* (2024) investigates the association between QoL of informal caregivers and the care they provide to adults with severe visual impairment through an SLR.[33] It found a negative association between the severity of patient visual impairment and caregiver anxiety, spousal strain, and intensity of informal care as well as a high prevalence of depressive symptomatology amongst caregivers.[33] This review shows that caregivers for adults with severe visual impairment have negatively impacted QoL. As part of further research, Lawrence *et al.* (2023) reported that carers for people with LHON stated they had financial difficulties, needed to change their routine and activities to accommodate care tasks, and limited time for leisure and hobbies. One carer even reported having to "cut ties with friends due to a lack of support and understanding".[32] This further demonstrates the importance of including caregiver disutility in the model. LHON impacts almost all aspects of patients' and caregivers' lives; activities of daily living, emotional functioning, relationships, studies, work, recreation and finances.[29] Due to the devastating nature of LHON to patients and the associated caregiver burden, it is essential to consider caregiver HRQoL in the base-case CEA. This was validated by both clinicians during the clinician validation interview conducted on 17th October 2024, who agreed that caregivers do experience a QoL decline when caring for LHON patients. One clinician strongly opposed the exclusion of caregiver disutility, as recommended by the EAG, calling it "*very critical and harsh to exclude caregiver disutilities".* The clinician further emphasised that "*LHON patients are typically young [adults], which can lead to complexities within families, as caregivers often experience guilt and must balance the support they provide to other children"* (Please refer to Appendix D for more details on the clinician validation).[6] In conclusion, 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

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	burden associated with caregiver HRQoL. This is supported by clinical experts, patient associations and literature. The revised company base-case is presented in Table 10.
8: Health state resource use	**The company strongly considers it appropriate to apply resource use costs for all health states, including patients with LogMAR <1. Costs are expected for patients in all health states, such as outpatient costs for low-vision aids, depression, and rehabilitation, which should not be disregarded. Furthermore, as validated by clinicians, patients are expected to accrue costs associated with supportive living for their entire lifetime.** The company base-case in the original submission, at the time of ACM1, included resource costs for each health state. Cost categories associated with blindness using Meads *et al.* 2003, which has been used to inform previous NICE appraisals for eye conditions (HST 11[23], TA 155[34], TA 294[24] and TA 274[7]). However, the proportion of patients accruing each resource use in each health state was informed using a KOL survey[35] as Meads *et al.* 2003 was not specifically based on people with LHON, but on patients with age-related macular degeneration. Through the KOL survey, each resource use estimates were populated by three international ophthalmologists and later validated by five UK clinical experts as part of this appraisal (CS, Appendix N). However, the EAG stated 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"* and "*in clinical practice, people who would incur health resource costs would be clinically visually impaired with a LogMAR of 1.0 to 1.3*" (Section 3.16 DGC). Therefore, the EAG preferred to apply resource costs only to people with LogMAR > 1, except depression costs, which were assumed to apply to all health states and using the proportion of patients requiring each resource to be taken directly from Meads *et al.* (2003). The company included a scenario analysis using data from Meads *et al.* (2003) during the clarification questions stage but did not consider it appropriate to assume that all patients with LogMAR < 1 do not require any resource use. The committee concluded that although the approaches were significantly different, they had a minor impact on the cost-effectiveness results and concluded that it was "*appropriate to apply the resource costs associated with outpatient visits (obtaining low-vision aids and rehabilitation) for health stages with LogMAR of less than 1*" (Section 3.16 DGC[14]). It is highly conservative to assume that only patients who are legally blind would accrue resource use costs. As stated in the company response to clarification question 16b), literature has shown that hospitalisation due to falls can occur to patients who are blind *and* to patients who are partially blind across all ages. The Royal National Institute of Blind People (RNIB) conducted research to estimate the number of falls due to partial sightedness and blindness in the UK using the methodology from Scuffham *et al.* (2002).[36] The report estimated that around 8,021 falls related to partial sightedness and blindness occurred in patients aged 18-59 in 2008, consisting of admitted, A&E, day cases, and ambulance fall types. The study also reports that half of fallers fall recurrently, which supports the regular application of hospitalisation costs. The company also agrees with the committee's conclusion that it is appropriate to "*apply the resource costs of outpatient visits (obtaining low-vision aids and rehabilitation) for health stages with a LogMAR of less than 1"* (Section 3.16, DGC[14]). The company would like to emphasise that due to the rarity of LHON and the limited literature available on health state resource use, the company had to seek the clinical opinion of three international ophthalmologists to obtain LHON-specific resource use estimates of each resource across the model health states. These estimates were subsequently validated by 5 UK clinical experts and therefore are robust values for

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	estimating resource use in UK clinical practice. During the UK clinician validation interviews, in August of 2023, one clinician stated that whilst the current resource use estimates are plausible, they would expect to see an approximate times two increase in outpatient care resource use due to the low number of vision clinics. The reason for the increase was the fact that with no treatment available there is little value to be gained from a clinic visit, therefore with the introduction of idebenone an increase is to be expected. Consequently, the company explored this uncertainty in the CEA at submission and found that the impact on the ICER was minimal, with the company's base-case ICER at submission increasing from £20,462 to £21,615 (an increase of £1,153). A recent clinician validation conducted on the 17th October 2024 further validated the healthcare resource use estimates (please see Appendix D for further details).[6] The clinicians were broadly in agreement with the estimates, consistent with the responses from the previous interviews conducted in August 2023. (Please see Appendix N for further details).[18] One clinician highlighted that there is no longer a blind registration fee to patients and strongly agreed with the company that supportive living costs should occur over a lifetime horizon and not as a one-off cost as proposed by the EAG. The same clinician also highlighted that they would expect costs associated with depression to occur over a much longer period of time instead of only as a one-off cost. However, to address EAG and committee's concerns regarding the uncertainty of the experts' estimates, the company conducted additional analyses, including: 1. **Scenario 1:** Midpoint estimates between the KOL survey and Meads *et al.* (2003) resource use inputs per health state. Please see Table 18, Appendix C for the resource inputs. 2. **Scenario 2:** Applying resource use inputs across all health states for the hospitalisation, depression and outpatient care costs only. For all other costs, resource use is only applied to patients with LogMAR>1. Inputs are informed using the KOL survey. Please see Table 19, Appendix C for the resource inputs. As demonstrated by the inputs for scenario 1 (midpoint estimates between the KOL survey and Meads *et al.* (2003), resource use is still estimated for patients with LogMAR<1, an accurate assumption for UK clinical practice, but it is by a smaller proportion than what was estimated by solely using the KOL survey (Table 18, Appendix C: Cost and resource use – patient proportions for scenario 1 and scenario 2). For example, only 1% of patients with LogMAR<0.3 and 3% of patients with LogMAR 0.3-1.0 accrue costs associated with hospitalisation. This proportion then remains below 20% for the remainder of the health states which is a conservative assumption given clinicians as part of the company's first validation (CS, Appendix N) stated outpatient care should be two times higher than the estimates given in the KOL survey. Furthermore, the proportion of patients receiving supportive living remains 5% and below for patients with LogMAR<1 which is also a conservative assumption given the input from clinical experts in the most recent clinical validation (17th October 2024; see Appendix D for further details), who stated that the proportion of patients receiving supportive living should be very high across all health states. Given the above, the company has updated the base-case to use scenario 1 – midpoint estimates between the KOL survey and Meads *et al.*(2003) – for informing the resource of patients with LHON in this CEA. The updated base-case ICER is £28,451 (please see Table 9 and Table 10 for further details). In order to address any uncertainty around the assumptions made in scenario 1, the company has also ran a scenario which assumes resource use is applied across all health

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	states for the hospitalisation, depression and outpatient care costs only, and for all other costs resource use is only applied to patients with LogMAR>1 and informed by the KOL survey (scenario 2) (Table 19, Appendix C: Cost and resource use – patient proportions for scenario 1 and scenario 2). This aligns with the literature that demonstrates that partially blind patients may still experience injurious falls and with the EAGs and committee's assumptions that resource use costs associated with outpatient visits (obtaining low-vision aids and rehabilitation) and depression which still occur in patients with LogMAR<1.[36] Applying scenario 2 to the company's updated base-case resulted in a decrease of the base-case ICER from £28,451 to £27,134, demonstrating that applying resource use only for patients with LogMAR>1 except for hospitalisation, depression and outpatient care costs increases the cost-effectiveness of idebenone. Furthermore, in order to also address the input from clinicians as part of the most recent validation (17th October 2024; see Appendix D for further details)[6], the company has also updated their base-case to assume a zero blind registration fee and that patients accrue costs associated with depression for 2 years. The zero blind registration fee assumes that the proportion of patients accruing this cost as part of the company's scenario 1 and new base-case are essentially cancelled and a 0% can be assumed across all health states for this cost category. The company's assumption that patients only accrue costs associated with depression is a substantially conservative assumption, given that one consulted clinician stated that depression is usually treated as an ongoing condition rather that a one-time occurrence and that patients don't need to be legally blind to experience depression. Furthermore, also in line with clinicians, the company strongly considers costs associated with supportive living should be applied across lifetime time horizon of the model. In conclusion, the company remains confident that it is appropriate to apply the resource use inputs to all health states and varying degrees of VA in order to accurately capture the economic burden of LHON to the NHS. The company's updates to the base-case from ACM1 include changing the proportion of patients accruing each resource use to a midpoint of the KOL survey and Meads *et al.* (2003) estimates (scenario 1), applying a £0 blind registration fee and assuming the cost of depression accrues over 2 years for patients with LHON. The company maintains their assumption that supportive living should occur over a patient lifetime, as supported by clinicians. The company is confident that these assumptions are the most suitable assumptions for this CEA whilst also addressing the concerns from the EAG and the committee.
9: Transition probabilities in the PSA	As highlighted by the committee and the EAG, the company did not vary transition probabilities in their probabilistic sensitivity analysis (PSA) as part of the original submission. The company instead varied the baseline distribution as a way of exploring the robustness of the transition probabilities. To address these concerns, the company has now added the functionality for the transition probabilities to be varied for both the idebenone and SoC treatment arms in the PSA. For the updated base-case, the company uses the SE values derived directly from the base-case transition probabilities from the integrated analysis (logistic model, MAR) for month 12 to month 36 and apply them to a beta tree variation method in the model. For SEs for the transition probabilities from baseline to month 12, an average SE value is calculated from the existing SEs. Results of the PSA using the company's updated base-case are presented in Table 11 and demonstrate a probabilistic ICER of £23,879. The ICER remains below the £30,000 WTP

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	threshold and demonstrates the robustness of the transition probabilities derived using the company' new updated integrated analysis.

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 ACM1

Economic input	Company's base-case at ACM1	Change(s) made in response to DGC
Changes in response to key issues		
Clinical effectiveness: idebenone	The clinical effectiveness of idebenone was modelled using several sources • **Baseline – month 6:** Transition probabilities derived from RHODOS RCT data • **Month 6 – month 36**: Transition probabilities derived from EAP data • **Month 36 onwards**: As a conservative assumption: no movement across health states	To address the concerns of the EAG and committee regarding limited data being available to model the idebenone and SoC clinical effectiveness, the company created an integrated analysis set and weighted analysis. The integrated analysis includes all available clinical data from different LHON studies (RHODOS, RHODOS-OFU, EAP, CaRS-I, CaRS-II, LEROS and PAROS), which is used in the weighted analysis to ensure the clinical effectiveness of idebenone and SoC is robustly modelled. In the new company base-case the clinical effectiveness of idebenone and SoC is modelled using several sources (as detailed in points 1-3 in response 1 [page 12]) • **Baseline – month 6:** Transition probabilities from baseline to month 6 are derived directly from data collected as part of the RHODOS RCT (as previously modelled) • **Month 6 – month 12**: Transition probabilities are derived from the integrated analysis 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 MAR assumption • **Month 36 onwards**: As a conservative assumption: No further movement is assumed for patients after month 36
Clinical effectiveness: SoC	The clinical effectiveness of SoC was modelled using several sources • **Baseline – month 6:** Transition probabilities derived from RHODOS RCT data • **Month 6 – month 36**: Transition probabilities derived from CaRS-I data • **Month 36 onwards**: As a conservative assumption: no movement across health states	
Time of treatment/ persistence	Persistence data were pooled from the RHODOS and EAP studies.	To ensure consistency in data sources for the clinical effectiveness and time on treatment, the modelling of treatment duration within the CEA is now informed using the time to indication to treatment discontinuation KM estimates based on the integrated analysis set.
Utility values	For the CEA base-case, patient utility values derived from Brown *et al.* (1999) have been used to inform HRQoL of patients with LHON.	The company models the patient HRQoL based on the HUI-3 values reported in the study by Lawrence *et al.* (2023) using values from the UK and ROI population.

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Economic input	Company's base-case at ACM1	Change(s) made in response to DGC
Changes in response to key issues		
Cost and resource use	The company base-case at ACM1 included the following cost and resource use assumptions: 1. Resource use based on inputs from a KOL survey 2. Blind registration cost assumed at £164.74 based on Meads et al (2003) inflated to 2022/23 3. Outpatient care costs applied across a lifetime time horizon 4. Supportive living costs applied across the lifetime time horizon 5. Depression costs applied as an annual one-off cost in the first year	The company's updates to the base-case from ACM1 are: 1. Resource use based on a midpoint patient proportion of KOL survey and Meads *et al.* (2003) estimates (scenario 1 [page 31]) 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
Additional changes		
[redacted]	[redacted]	[redacted]
Model corrections		
Application of age-adjusted utilities	The company base-case at ACM1 included a minor error in the way age-adjusted utilities had been applied in the CF health state within the Trace Sheets of both treatment arms.	The company has corrected this minor error within the CEM and it is now included in the updated base-case analysis. The impact of this correction on the results is negligible. Please note that this may explain some differences in the company and EAG's base-case ICERs from the previous CEM version from the EAG's report (V3.0) to the most up-to-date CEM version submitted alongside this DGC response (V4.0).

Abbreviations: ACM1 – First appraisal committee meeting; CEA – Cost-effectiveness analysis; CF – Counting fingers; DGC – Draft guidance consultation; EAG – External assessment group; EAP – Expanded access programme; HRQoL – Health-related quality of life; KOL – Key opinion leader; LHON – Leber's hereditary optic neuropathy; MAR – Missing at random; [redacted]; PS – Propensity score; RCT – Randomised controlled trial; ROI – Republic of Ireland; UK – United Kingdom

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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]	28,451

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 4 and Figure 5 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]	23,879

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 4: 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 5: 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 6.

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 - CF	[redacted]	[redacted]
Carer utility - LogMAR 1.3-1.7	[redacted]	[redacted]
Patient utility - LogMAR 0.3-0.6	[redacted]	[redacted]
Carer utility - CF	[redacted]	[redacted]
Patient utility - LogMAR 1.0-1.3	[redacted]	[redacted]
Residential care cost (£)	[redacted]	[redacted]
Carer utility - LogMAR 1.0-1.3	[redacted]	[redacted]
Patient utility - LogMAR 0.6-1.0	[redacted]	[redacted]

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

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Figure 6: OWSA tornado diagram (revised company base-case, [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]	**28,451**
Clinical inputs - Integrated data	1	Logistic model, MAR (in both treatment arms)	Logistic model, MNAR (in both treatment arms)	[redacted]	[redacted]	25,378
	2		Weighted observed, MAR (in both treatment arms)	[redacted]	[redacted]	28,735
	3		Weighted observed, MNAR (in both treatment arms)	[redacted]	[redacted]	25,908
Utility source	4	Lawrence *et al.* (2023) – HUI*	Lawrence *et al.* (2023) – EQ-5D-5L*	[redacted]	[redacted]	40,666
	5		Lawrence *et al.* (2023) – TTO*	[redacted]	[redacted]	34,057

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Parameter	Scenario number	Base-case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
	6		Brown *et al.* (1999)	[redacted]	[redacted]	41,544
	7		Czoski-Murray (2009)	[redacted]	[redacted]	36,205
	8		Rentz *et al.* (2014)	[redacted]	[redacted]	39,470
Resource use source	9	Scenario 1: Midpoint values of KOL survey and Meads *et al.* (2003)	KOL survey	[redacted]	[redacted]	27,604
	10		Meads *et al.* (2003)	[redacted]	[redacted]	29,299
	11		Scenario 2: KOL survey (alternative scenario at DGC)	[redacted]	[redacted]	27,134
Resource use costs	12	Blind registration cost of £0	Blind registration cost of £165	[redacted]	[redacted]	28,439
	13	Depression costs applied for 2 years	1 year	[redacted]	[redacted]	28,461
	14		Lifetime	[redacted]	[redacted]	28,234

* - averaged from the UK and ROI population.
Abbreviations: HUI - Health utilities index; ICER - Incremental cost-effectiveness ratio; MAR – Missing at random; MNAR – Missing not at random; PAS - Patient access scheme; QALY- Quality-adjusted life years; ROI – Republic of Ireland; TTO – Time trade off; UK – United Kingdom

Table 14: Scenario analysis (revised company base-case, [redacted]) – EAG's preferred 4 health state structure

Parameter	Scenario number	Base-case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
Base-case				[redacted]	[redacted]	**32,698**
Clinical inputs - Integrated data	1	Logistic model, MAR (in both treatment arms)	Logistic model, MNAR (in both treatment arms)	[redacted]	[redacted]	28,369
	2		Weighted observed, MAR (in both treatment arms)	[redacted]	[redacted]	32,627
	3		Weighted observed, MNAR (in both treatment arms)	[redacted]	[redacted]	28,345

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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- Complete the disclosure about links with, or funding from, the tobacco industry.
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Appendix A: Reasons for exclusion from the ITT population

Table 15: Reason for exclusion from the ITT population - integrated analysis set

Study	Reason for excluding from ITT population														
	DRA status unknown	Data Integrity Concerns	No baseline data	No post-baseline data	Not LHON indication	Subject enrolled in CaRS-I	Subject enrolled in CaRS-II	Subject enrolled in PAROS	Subject enrolled in PAROS – mapping not possible	Subject enrolled in RHODOS	Subject not dosed	Subject not dosed or dosed with unknown/ unusual dose or period	Subject not enrolled	VA not accurate at baseline/ V4	Total
CaRS-II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RHODOS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CaRS-I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PAROS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LEROS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Appendix B: Transition probabilities

Logistic model - MAR
Idebenone

Table 16. Transition probabilities derived from the logistic model – MAR - Idebonone – Company's original 8 health state model structure

6-months -> 12-months

	Transition to							
Transition from	LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6-1.0	LogMAR 1.0-1.3	LogMAR 1.3-1.7	CF	HM	LP
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CF - Counting fingers; HM - Hand movement; LP - Light perception

12-months -> 18-months

	Transition to							
Transition from	LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6-1.0	LogMAR 1.0-1.3	LogMAR 1.3-1.7	CF	HM	LP
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CF - Counting fingers; HM - Hand movement; LP - Light perception

18-months -> 24-months

	Transition to							
Transition from	LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6-1.0	LogMAR 1.0-1.3	LogMAR 1.3-1.7	CF	HM	LP
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CF - Counting fingers; HM - Hand movement; LP - Light perception

24-months -> 30-months

	Transition to							
Transition from	LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6-1.0	LogMAR 1.0-1.3	LogMAR 1.3-1.7	CF	HM	LP
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CF - Counting fingers; HM - Hand movement; LP - Light perception

30-months -> 36-months

	Transition to							
Transition from	LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6-1.0	LogMAR 1.0-1.3	LogMAR 1.3-1.7	CF	HM	LP
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CF - Counting fingers; HM - Hand movement; LP - Light perception

SoC

Table 17. Transition probabilities derived from the logistic model – MAR - SoC – Company's original 8 health state model structure

6-months -> 12-months

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]

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	Transition to							
Transition from	LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6-1.0	LogMAR 1.0-1.3	LogMAR 1.3-1.7	CF	HM	LP
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CF - Counting fingers; HM - Hand movement; LP - Light perception

12-months -> 18-months

	Transition to							
Transition from	LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6-1.0	LogMAR 1.0-1.3	LogMAR 1.3-1.7	CF	HM	LP
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CF - Counting fingers; HM - Hand movement; LP - Light perception

18-months -> 24-months

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

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	Transition to							
Transition from	LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6-1.0	LogMAR 1.0-1.3	LogMAR 1.3-1.7	CF	HM	LP
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CF - Counting fingers; HM - Hand movement; LP - Light perception

24-months -> 30-months

	Transition to							
Transition from	LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6-1.0	LogMAR 1.0-1.3	LogMAR 1.3-1.7	CF	HM	LP
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CF - Counting fingers; HM - Hand movement; LP - Light perception

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

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30-months -> 36-months

	Transition to							
Transition from	LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6-1.0	LogMAR 1.0-1.3	LogMAR 1.3-1.7	CF	HM	LP
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CF - Counting fingers; HM - Hand movement; LP - Light perception

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

Draft guidance comments form

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Appendix C: Cost and resource use – patient proportions for scenario 1 and scenario 2

Table 18: Cost and resource use - Scenario 1 - midpoint estimates between the KOL survey and Meads *et al.*

Resource	LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6 - 1.0	LogMAR 1.0 - 1.3	LogMAR 1.3 - 1.7	CF	HM	LP
Hospitalisation	1%	3%	3%	12%	12%	16%	16%	16%
Outpatient care	7%	30%	30%	53%	53%	53%	53%	53%
Community care - Blind registration	0%	26%	26%	97%	97%	97%	97%	97%
Community care - supportive living	0%	5%	5%	25%	25%	35%	35%	35%
Residential care	0%	2%	2%	19%	19%	28%	28%	28%
Depression resulting from LHON	23%	32%	32%	38%	38%	47%	47%	47%

Abbreviations: CF - Counting fingers; HM - Hand movement; KOL – Key opinion leader; LHON - Leber hereditary optic neuropathy; LP - Light perception

Table 19: Cost and resource use - Scenario 2 - applying resource use inputs across all health states for the hospitalisation and outpatient care costs only. For all other costs, resource use is applied to patients with LogMAR>1 only and informed using the KOL survey

Resource	LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6 - 1.0	LogMAR 1.0 - 1.3	LogMAR 1.3 - 1.7	CF	HM	LP
Hospitalisation	2%	3%	10%	18%	20%	22%	27%	30%
Outpatient care	13%	38%	80%	83%	83%	83%	83%	83%
Community care - Blind registration	0%	0%	0%	100%	100%	100%	100%	100%

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Community care - supportive living	0%	0%	0%	40%	48%	57%	63%	70%
Residential care	0%	0%	0%	7%	8%	20%	22%	35%
Depression resulting from LHON	7%	20%	30%	33%	42%	45%	58%	65%

Abbreviations: CF - Counting fingers; HM - Hand movement; KOL – Key opinion leader; LHON - Leber hereditary optic neuropathy; LP - Light perception

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

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Appendix D: Clinician validation report (17th October 2024)

Please find Appendix D attached as a separate document to this response.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions

[18/12/2024]

File name	Version	Contains confidential information	Date
ID547 Idebenone clarification on DG response to PM for company_company comments [REDACTED] 18Dec24	**V1.0**	**Yes**	**18th December 2024**

Section A: Clarification on effectiveness data

Multiple imputation and MMRM

A1. Priority question. In relation to change from baseline in best BCVA presented in the Integrated Statistical Analysis Report please:

a) **clarify whether a Missing At Random (MAR) approach is used in Table 11 of Integrated Statistical Analysis Report (change from baseline in best BCVA- weighted MMRM);**
b) **clarify whether a different form of MAR is used in Table 12 (change from baseline in best BCVA-weighted MMRM-MAR) and explain the differences between the models used between Table 11 and Table 12 (Integrated Statistical Analysis Report);**
c) **comment on why the magnitude of the treatment effect and uncertainty (standard errors) considerably differ between Table 11 and Table 12 (Integrated Statistical Analysis Report).**

Response to question A1 a):

Both Mixed Model Repeated Measures (MMRM) and Multiple Imputation (MI) methods are based on the assumption of missing at random (MAR) and are model-based approaches suggested by the EMA's Guideline on Missing Data in Confirmatory Clinical Trials and US National Research Council: "The Prevention and Treatment of Missing Data in Clinical Trials".[1] The US FDA has not issued any guidance on handling missing data in clinical trials, but it generally follows the guidelines from the National Research Council.

As per the SAP Section 7.1.3 the MMRM has been run using a traditional approach with no imputation as a first step.[2] The results are presented in Table 11 of the Statistical Report. As the MMRM has an implicit approach of MAR, i.e. does not explicitly impute the missing values, but rather assumes that the patient's missing data after withdrawal would have followed the trend of his or her own treatment group, the results in Table 11 are based on a MAR approach.[3]

Response to question A1 b):

In our integrated analysis MAR and Missing Not At Random (MNAR) MI has been performed for sensitivity analysis, creating complete case datasets that have been

then analysed by the same MMRM model. Results are presented in Table 12 and Table 13, respectively.[3]

As described in the SAP Section 7.1.2, MI approach involves three steps:

a) The missing data are imputed m times to generate m complete data sets,
b) Each of the m complete datasets are then analysed using the statistical method for the previously specified endpoint (MMRM),
c) The results from the m complete data sets are then combined for inference.[2]

It has been demonstrated by Siddiqui (2011) that higher variability is expected in MI method, because missing data are filled in many times, with many different plausible values estimated for each missing value, creating more variability. In this paper a discussion on comparison of the MMRM vs MI is presented.[4]

Response to question A1 c):

In Siddiqui (2011) it has also been demonstrated how higher variability is expected in MI method, because missing data are filled in many times, with many different plausible values estimated for each missing value, thereby creating more variability.[4]

For the same reasons as described in response to question A1 b) above, differences in estimates might be observed. The distribution based on simulated data can lead to a different regression model, leading to varying estimates that differ between models.

However, it must be noted how this difference is not biased in favour of any treatment group, the estimated difference of idebenone vs SoC (and corresponding SE) are similar to the estimates from MMRM without MI.

A2. Priority question. The EAG notes that the magnitude of the effect of idebenone is substantially reduced when using a Missing Not At Random (MNAR) model, while uncertainty is increased (Table 13, Integrated Statistical Analysis Report). Thus, the EAG is critically concerned that the company has opted for a MAR approach with no tests carried out to determine if data were MAR. Please:

a) present the results of relevant tests to support the MAR assumption holds;

b) comment on the reduced effect of idebenone where the MNAR approach is used;
c) elaborate on why the current (MAR) baseline model for change in best BCVA was selected over MNAR.

Response to A2

The MMRM analysis uses an implicit imputation of missing values under a MAR assumption. To aid the EAG's analysis, the company performed additional sensitivity analyses with different imputation methods to investigate the robustness of the results.

The results of the (primary) MMRM analysis is presented in Table 11 of the statistical report. The two sensitivity analyses included an MMRM using an explicit MAR approach and an MMRM using a MNAR approach, with results presented in Table 12 and 13 of the statistical report, respectively.[3] A detailed description of the imputation process used is included in section 7.1.2 of the SAP.[2] The results in Table 12 and Table 13 should be compared in order to assess the impact of different missing data assumptions.

When comparing the results presented in Table 12 and Table 13, the magnitude of the effect is comparable, whereas the uncertainty has slightly increased. This indicates that the results presented in Table 11 are robust regardless of the missing data observed.

As described in the paper by Siddiqui (see reply to question A1), higher variability can be expected when using MI methods.[4] No test has been carried out on the MAR assumption, as there is no consensus on which type of test can be performed. Therefore, to support the EAG's analysis the company have presented all the data and have showed that the results are not considerably different in terms of clinical efficacy of idebenone vs SoC. Moreover, the MI MNAR approach yields more positive results for idebenone than the MI MAR assumption, (although with slightly higher variability).

A3. Priority question. The EAG notes that no imputation was performed for the analysis of best BCVA before the 12-months analysis visit.

a) **Please clarify why multiple imputation was performed only from 12-months onwards.**
b) **Please clarify the number, and proportion, of patients for whom data was imputed at each time-point (i.e., 6 months through to 48 months).**
c) **Please provide analysis results using matched patients baseline best BCVA and final follow-up visit without imputation.**

Response to A3. a)

In the natural history of LHON, after onset, disease progression is expected to be characterised by a quick deterioration until the nadir, followed by a slow stabilisation with some cases of spontaneous improvement. For this reason, the assumption of linearity of BCVA cannot be made in the first months after baseline.

Hence, all the assessments included up to the 6 Month analysis visit have to be analysed separately from the assessments at the 12 Month analysis visit onwards. As our model is based on a regression model including all the known prognostic factors, the lack of linearity makes multiple imputation unfeasible for the time period up to 12 months.

Response to A3. b)

The pattern of missing data is shown in *OUTPUT_17_MISSINGNESS_PATTERN* of the integrated statistical analysis report.[3]

In this table, each “group” represents a set of observations that share the same pattern of missing information. For example, group 1 represents the [redacted] patients that have complete information on all variables of interest, while group 2 and 3 represents the [redacted] and [redacted] patients with missing value just for Analysis Visit Month 48 and 42, respectively. This table is also useful to recognize different missingness patterns such as monotone missing or non-monotone missing. Monotone missing pattern can be observed in longitudinal data when a patient drops out at a particular time point and therefore all data after that is subsequently missing. On the contrary, the non-monotone missing

pattern can be observed when a patient skips just a visit but has an observation before and after. The imputation of the monotone missing data is more impacting than the imputation of the non-monotone missing data since the trajectory of the non-monotone missing data can be predicted by data available before and after the data point that is missing.

In our integrated analysis, as per SAP Section 7.1.2, MI has been applied with two different models for the non-monotone and monotone missing data. Additionally, the table below summarises the number of patients with at least one assessment at each timepoint by treatment group in the analysis set used for the change in best BCVA in LogMAR and CRB, i.e., all ITT patients with at least one assessment on or after the Month 12 analysis visit. In this analysis, assessments in the RHODOS-OFU study have been included for the SoC arm only. Idebenone patients have not been included, since they are no longer on treatment. A total of [redacted] Idebenone patients and [redacted] SoC patients were included.

Table 1: Number of patients with at least one assessment at each timepoint by treatment group in the analysis set used for the change in best BCVA in LogMAR and CRB

Frequency	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48+
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CRB – Clinically relevant benefit; SoC – Standard of care

Best BCVA in LogMAR has been analysed as per the reply to question A1 using MMRM (with no explicit imputation) and MI. With regards to MI the number of patients with data available must be read in conjunction with the presented missing pattern. We acknowledge that the percentages of patients with data for some of the timepoints is limited, however as per the previous request from the EAG, different types of imputation techniques have been explored and results have been shown to be consistent. This provides sufficient confidence that the unobserved assessments do not impact the robustness of the company's conclusions.

Response to A3. c)

The company do not agree with the analysis suggested by the EAG. The integrated studies have a considerable difference in the follow-up of the enrolled patients. If for each patient the baseline and the final follow-up visits are taken into account, there

will be a substantial difference in the time between the final visit and baseline. For some patients, due to the nature of the natural history cohort, the final visit could be at 3 months, whereas for others it may be after several years. In the approach suggested by the EAG approach, this will not be taken into account.

Merging results from different timepoints will introduce a huge variability. Furthermore, these results will not have a meaningful interpretation, from both a statistical and clinical perspective.

Propensity score weighting analysis

A4. Priority question. The EAG is concerned that the Company has excluded all assessments from the RHODOS study in the analyses run on assessments (including the 6-month assessments) due to RHODOS being a randomised controlled trial (RCT).

a) **Please elaborate on the rationale for excluding the RHODOS data.**
b) **Please clarify why assessments up to 6-months were analysed separately from assessments from 12-months onwards.**

Response to A4

The company would like to clarify that RHODOS data have **not** been excluded. RHODOS data have been included in the economic model: the transition probabilities for the period 0-6 months have been derived based on RHODOS data. As RHODOS is a randomised controlled trial (RCT), the data from this trial should take priority over other synthesised data

Integration of the RHODOS data with data coming from study of different design is not appropriate due to the methodological differences between the study types which would introduce bias. In particular, for the SoC group used in the integration, this would correspond to assume no placebo effect and equal results for patients receiving no treatment as compared to patients receiving placebo.

In addition, the high component of personal involvement in standardised assessments combined with a strict follow-up through an interventional study contrasts to data from untreated patients originating from a registry and leads to potential differences in data robustness.

Furthermore, the natural history of LHON shows that after disease onset, a quick deterioration is observed that leads to a nadir. After nadir, a spontaneous (partial) recovery is possible. As a result, there is no linearity in the data collected during the first period after onset of the disease. Therefore, a different approach in the analysis of the data is needed for the first 6 months as compared to the period afterwards.

A5. Priority question. The EAG is concerned that the Company has not analysed 6-month data alongside all other time points and that data from the RHODOS RCT have been excluded. Accordingly, it is unclear as to whether the 6-month results of the RHODOS trial align with the 6-month results of the integrated analysis. As such, please provide the following:

a) **Analysis and results of the 6-month analysis for the RHODOS RCT;**
b) **Analysis and results of the integrated analysis where 6-month data has been analysed alongside all other timepoints (excluding the RHODOS RCT);**
c) **Analysis and results of the integrated analysis where 6-month data has been analysed alongside all other timepoints (including the RHODOS RCT);**
d) **Clarification as to whether the results of the 6-month results for the integrated analysis align with, or differ from, the 6-month results of the RHODOS RCT;**
e) **For the points a) through c) please provide results for best BCVA using the baseline, MAR sensitivity, and MNAR sensitivity approaches. For CRB, please provide results using the weighted logistic regression approach. For CRR, please provide results using the KM product limit method;**
f) **Please provide assessment figures where new propensity-score matching (PSM) has been performed for the above analyses.**

Response to A5. a)

The clinical efficacy results of the RHODOS RCT are included in the Clinical Study Report of this study. This report has been provided to the EAG as part of the company submission.

Response to A5. b)-f)

As per the company's response to question A3.a, the natural history of LHON makes the assumption of linearity of data in the first 6 months unlikely. As this assumption is the basis of the analysis performed by the company, it is not possible to present results of BCVA data for the first 6 months, i.e., MMRM, MI MAR and MNAR cannot be run due to lack of linearity. Therefore, the requested analyses in a) through f) have not been performed.

The results on CRR using the KM product limit method, as requested, are included in the Statistical Report Section 5.3.4. The analysis has been performed on the analysis set 3, including all ITT patients and data since baseline. RHODOS data have not been integrated for the reasons highlighted in the company's response to question A4.

Participant matching

A6. Priority question. Please clarify whether matching was performed to align the baseline characteristics in the integrated analysis to those in the RHODOS trial, or whether matching was performed solely to align the baseline characteristics between the arms of the integrated analysis.

Matching was performed solely to align the baseline characteristics between the treatment groups of the integrated analysis.

As per SAP (Section 7.1.1), different types of analyses have been done considering different time periods.[2] For this reason, the PS model has been run on baseline characteristics of three different sets of patients:

- SET 1: All ITT patients with at least one assessment at 6 Months or 12 Months analysis visit, excluding those enrolled in the RHODOS study.

- SET 2: All ITT patients with at least one assessment on or after 12 Months analysis visit. In this analysis, assessments in the RHODOS follow-up will be included for the SoC ARM only. Idebenone patients will not be included since they were no longer on treatment.

- SET 3: All ITT patients, excluding those enrolled in the RHODOS study.

For each type of analysis, the applicable set has been taken into consideration and matching was performed. In doing so, the comparability between the groups was maximized for each set and consequently for each analysis involving this particular set.

A7. Please confirm whether matching of participants was performed at baseline and their available observations across analysis time points (+/- 3 months) were used henceforward (meaning the same patients were followed up overtime), as opposed to matching eyes at available follow-up times with the matching algorithm being performed *de novo* at each time point.

Matching was performed considering the patient's baseline characteristics. The same weight has been maintained across all subsequent analysis time points.

A8. The EAG notes that its clinical experts have previously outlined that visual acuity at nadir is a potential prognostic factor. While other potential prognostic factors have been accounted for in the PSM analysis, visual acuity at nadir has not been considered. Please justify the exclusion of this potential prognostic factor or provide analysis results of the PSM analysis where visual acuity at nadir has been accounted for.

The company acknowledge the importance of patients' nadir. Since the data has been collected in a non-controlled way, using a registry, there are no standard timepoints and it is not possible to assess if nadir occurred within the observed time period, or to identify when exactly the nadir happened (this could be between assessments).

Although the registry studies foresaw the collection of retrospective studies the schedule of the visits is random (non-interventional study). This can bias the nadir values, as patients with less severe disease or in the early stage of disease will be more willing to visit the site (in case patients are legally blind they might not visit the site frequently). Furthermore, for the idebenone patients, not all the studies allowed retrospective collection of data. In LEROS, for example, there are no retrospective collection of assessments on visual acuity. This means that for all those patients coming into the study with a time from onset of more than 12 months the nadir is likely to be missed.

Though the company agrees with the EAG that nadir is an important potential prognostic factor, the above response explains the limitations of the data collected,

which makes it unfeasible to take the nadir into account. While for those patients with recent onset, the nadir might be collected, however the value will be impacted by idebenone treatment, for which different studies have shown positive results in preventing severe deterioration of the disease.

Baseline characteristics

A9. Please specify if baseline characteristics reported in Table 1 (Company's response) correspond to the ITT population (N=847). If not the ITT population, please provide further details on the population that these baseline characteristics relate to.

Table 1 in the Company's response to DGC presents summary statistics (weighted by PS weights) on the SET 2 patients, that was used for the MMRM and MI modelling.

SET 2 consists of all the ITT patients with at least one assessment on or after the Month 12 analysis visit. In this analysis, assessments in the RHODOS-OFU study have been included for the SoC arm only. Data for idebenone patients from RHODOS-OFU have not been included, since they are no longer on treatment. A total of [redacted] idebenone patients and [redacted] SoC patients have been included. SET 2 has been used in assessing the clinical efficacy in all models where the assumption of linearity is needed. PS weights have been computed for a total of [redacted] idebenone patients and [redacted] SoC patients. One patient in the SoC was excluded since age was missing and the PS weights have not been computed.

A10. Please provide a breakdown of the number of participants from each study (RHODOS, RHODOS-OFU, EAP, CaRS-I, CaRS-II, LEROS and PAROS) included in each arm of Table 1 in the Company's response.

Table 2 presents the requested distribution of patients by treatment group and study.

Table 2: The number of participants from each study included in each arm of the Company's

response

	Idebenone, N (%)	SoC, N (%)	Total, N (%)
SNT-CRS-002	[redacted]	[redacted]	[redacted]
SNT-EAP-001	[redacted]	[redacted]	[redacted]
SNT-II-003	[redacted]	[redacted]	[redacted]
SNT-IR-006	[redacted]	[redacted]	[redacted]
SNT-IV-003	[redacted]	[redacted]	[redacted]
SNT-IV-005	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Abbreviations: SoC – Standard of care

A11. Please clarify if where the reason for exclusion from the ITT reads 'subject enrolled in CRSI/RHODOS' etc (Table 9, Integrated Statistical Analysis Report), means patients were excluded because they were enrolled in more than one study.

The EAG is correct in their understanding that patients have been excluded due to their enrolment in more than 1 study. Section 3.2 (Table 3) of the Statistical Report provides more details on the inclusion of patients in the ITT populations per study.

Outcomes

A12. Please elaborate on the following points with regards to the off-chart LogMAR values:

a) **How was the scale for the off-chart LogMAR values chosen, as the EAG notes that multiple different scales have been presented within previous literature.[5]**

b) **There is a consistent difference in LogMAR of 0.3, between the off-chart values of 'Finger count', 'Hand motion', and 'Light perception'. However, there is a difference in LogMAR of 0.55 between 'Light perception' and 'No light perception'. Would the discrepancy in differences between off-chart categories be considered clinically appropriate for this analysis?**

Response to A12 a).

The company acknowledge there are multiple different scales and there is no consensus in the field. Given that the primary purpose of our analysis is to create data

to inform the economic model, as per SAP Section 3.2.1, the selected values for the off-chart categories are the mid-point of the logMAR ranges that have been included for the health states used in the cost-effectiveness model. One of the advantages of this approach is to have off-chart imputed (by MI) values balanced among the logMAR values included in each health state.

Response to A12 b).

As mentioned in the response to A12 a). there is no standardised logMAR value attributed to the off-chart health states in the literature, therefore our analysis made use of the midpoint value from the specified health state categories to address this issue. For the No Light Perception (NLP), we have used LogMAR 3.0, which is frequently used in literature. We would like to highlight that the only impact of this imputation for the NLP visual level on the overall analysis is on the MMRM and MI datasets run on the analysis SET 2. In this set, there are only [redacted] patients with an NLP imputed as LogMAR 3.0 as best corrected visual acuity.

Please note that given that the NLP health state in not included in the cost-effectiveness model, this has no bearing on the economic evaluation.

A13. Please clarify if in unilateral patients, best BCVA was measured only in eyes affected by LHON.

Patients with unilateral involvement at baseline were measured in both eyes in the studies, but only data from the affected eye at baseline have been included in the analysis.

A14. The statistical analysis plan outlines that the conditions for determining whether a patient achieves a CRB or CRR are based on a patient's baseline best BCVA. As such, for each of the different criteria (for both CRB and CRR across individual treatment arms), please provide the number of patients who fall under each category (e.g. baseline best BCVA <1.7 logMAR) according to baseline BCVA and the number of patients, for each category, who were deemed to have a CRB or CRR.

The company would like to clarify a couple of points:

1. All our analyses have been performed based on PS weights. This means that the resulting observations are patients' weights and not actual patients. For this reason,

it's not possible to present number of patients according to any classification. See Section 7.1.1 of SAP.[2]

2. CRB/CRR analyses have been done based on MI datasets. Hence, the number of patients with CRB/CRR at each visit is not necessarily corresponding to the number of observed patients and could also include imputed results. See Section 7.1.2 of SAP.[2]

For these reasons, the company believe that the analysis requested gives no additional value to the summaries already presented (Table 14 and 15 of Statistical Report).[3]

A15. Please provide the number of patients, at each timepoint and in each treatment arm, who had BCVA assessed through use of a Snellen chart, which was subsequently converted to logMAR.

Conversion from measurements using a Snellen chart to logMAR is validated and widely used. In our analyses, we have converted all data collected using the Snellen methodology and the original collected values (plus methodology) were not carried over to the integrated datasets that have been used for the current analysis.

Adding this data at this stage would require a considerable amount of time and the added value is expected to be negligible.

A16. Priority question. For all outcomes of the current integrated analysis available (change in best BCVA in LogMAR, CRB, Time to first CRR) and any additional requested analyses provided, please provide:

a) **the sample size for idebenone and standard of care (SoC) arms at each time point.**
b) **the number and proportion of participants with imputed data at each time point, by arm for change in best BCVA in LogMAR.**

Response to A16 a).

For the analysis of change in best BCVA in LogMAR and CRB, as per SAP, analysis SET 2 have been considered, which consists of all ITT patients with at least one assessment on or after the Month 12 analysis visit. In this analysis, assessments in

the RHODOS-OFU study have been included for the SoC arm only. Idebenone patients from RHODOS-OFU have not been included, since they are no longer on treatment.[2]

A total of [redacted] idebenone patients and [redacted] SoC patients have been included.

The first two tables contained in the OUTPUT_14_MMRM_WEIGHTED summaries the number of patients with at least one assessment at each timepoint in idebenone and SoC respectively.

Response to A16 b).

Best BCVA in LogMAR has been analysed as per the reply to question A1 using MMRM (with no explicit imputation) and MI. With regards to MI, as per the reply to question A3.b, the number of patients with data available must be read in conjunction with the presented missing pattern. We acknowledge that the percentages of patients with data for some of the timepoints are limited, however as per the previous request from the EAG, different types of imputation techniques have been explored and results have been shown to be consistent. This provides sufficient confidence that the unobserved assessments do not impact the robustness of the company's conclusions.

Please note that for the time to CRR analysis, as per SAP, SET 3 of patients have been used, since no linearity assumption was needed.[2] SET 3 consists of all ITT patients, excluding those enrolled in the RHODOS study. A total of [redacted] idebenone patients and [redacted] SoC patients have been included. No imputation has been done. All the visual acuity results have been included in the analysis according to their assessment date, regardless of the Analysis Visits they have been classified.

A17. The EAG is concerned that the baseline date varies across studies (for example, baseline is RHODOS/LEROS/EAP is the first visit before exposure while for CaRS-I/II it is the date of the earliest BCVA assessment).

a) **Please comment on how differences in 'baseline' across studies were accounted for in the matching of participants and the analyses (including**

the analyses for CRB) to ensure patients were matched at the same timepoint in their disease stage;

b) Please provide data on change in best BCVA (using a MNAR model) and time to first CRR from 'nadir' and 'disease onset'.

Response to A17 a).

The different definition of baseline is a natural consequence of the integration of different studies with different designs. The SoC data are from a registry of untreated patients, while the RHODOS, LEROS, and EAP are studies that foresee the start of the treatment under analysis at the study entry.

In the integrated analysis, the disease stage has been included in terms of visual acuity at baseline and time from onset. Both of these prognostic factors have been included in the computation of the PS weights and also in each of the analysis models as covariates/regression factors, as specified in the SAP.[2] As the treatment groups are comparable in terms of the PS weight, it can be assumed that the baseline differences have been accounted for.

Response to A17 b).

Due to the nature of data collection in our studies, data on nadir are either not present or unreliable. Therefore, the company considers any type of nadir analysis unrealistic and potentially biased. See also reply to question 8a).

With regard to the analysis based on disease onset, the company would like to point out that the period between disease onset and the baseline, as considered in our studies, will be an untreated period for which no details are available in most of the patients in our datasets.

A18. Please confirm whether any formal framework (e.g., the Delphi method or Sheffield Elicitation Framework) was used when eliciting feedback from clinical experts?

Given the nature of the company's clinician validation, the Delphi method or Sheffield Elicitation Framework was not needed. Instead, a structured meeting approach was used, involving one interview with two clinician experts via a Teams meeting,

supported by a detailed PowerPoint presentation to guide and facilitate the discussion. All information on how the validation was conducted can be found in Appendix D of the company's response to the DGC. This approach is commonly used and was also employed as part of the original company submission (CS, Appendix N), in which the committee and the EAG raised no concerns.

A19. The EAG notes there is a discrepancy between the values reported in Table 1 of the company's response (baseline characteristics from the weighted analysis) and those reported on page 66 in Statistical Analysis report document B (Descriptive WEIGHTED stats of Gender, Age at First Onset, Time from First Onset at Bsl, Bsl Best BCVA, Eyes Involved at Bsl, Mutation. Integrated ITT. Pts with at least one assessment in Analysis Visit 12 Month [+/- 3 Months] or after).

Table 10 of the Statistical Report presents demographic characteristics for the ITT population. While Table 1 of the company's response, as per reply to question A9, is on a specific analysis set.

Complete summary statistics for the demographic characteristics, weighted and unweighted, for each of the analysis set used in the analysis, are in the statistical outputs. Namely:

SET 1: OUTPUT_09_PSMODEL_SAMPLES_WEIGHTED_6_12, OUTPUT_09_PSMODEL_SAMPLES_UNWEIGHTED_6_12

SET 2: OUTPUT_12_PSMODEL_SAMPLES_WEIGHTED, OUTPUT_12_PSMODEL_SAMPLES_UNWEIGHTED

SET 3: OUTPUT_34_PSMODEL_SAMPLES_WEIGHTED_TTE, OUTPUT_34_PSMODEL_SAMPLES_UNWEIGHTED_TTE

A20. Priority Question: The EAG notes that in Tables 12 and 13 of the Integrated Statistics Report, the standard errors associated with the estimated difference in best BCVA are much smaller than the standard errors associated with the change from baseline in best BCVA for the individual treatment arms. The EAG would expect that the uncertainty associated with the estimated difference would be greater than the uncertainty associated with the change from baseline in best BCVA for the individual treatments (as seen in Table 11). The EAG notes

that there are limited details in the SAP regarding how the estimated difference (including standard errors, confidence intervals, and p-values) were calculated. As such, can the company please provide the following:

- **A description of the methods (e.g., t-test etc) used to calculate the estimated difference (including associated standard error, confidence intervals, and p-values).**

- **An example calculation for one time point from either the MI MAR or MI MNAR analyses (e.g., month 12 of the MI MNAR analysis [Table 13]).**

- **A discussion of why the uncertainty associated with the estimated difference for the MI MAR (Table 12) and MI MNAR (Table 13) analysis is less than the uncertainty for the estimated change for the individual treatments (including why this was not observed for the baseline MMRM analysis [Table 11]).**

1. **Description of methods:**

As per Statistical Analysis Plan, Section 9.1, SAS version 9.4 has been used to perform all the statistical analyses.

Table 11 of the Statistical Analysis Report presents the results obtained from the PROC MIXED procedure.

The MMRM model included treatment group (variable ARM), analysis visit (variable AVISITn), treatment-by-analysis-visit interaction (variable ARM*AVISITn), gender (variable SEX), LHON mtDNA mutation (variable MUTCD), time from onset at baseline (variable BLTFON), best BCVA at baseline (variable BASE), as fixed effects, and the baseline best BCVA-by-analysis-visit interaction (variable BASE*AVISITn) and it was weighted by the stabilised inverse probability of treatment weights computed by the PS model (WEIGHT _ATEWgt_). Restricted maximum likelihood estimation was used (method=reml). An unstructured covariance matrix was used to model the within-subject error (type=un) and the Kenward-Roger approximation was used to estimate the degrees of freedom (ddfm=kr). Regarding the model (we apologise for not properly commenting in the statistical analysis report), laterality has not been included since unilateral involvement was reported

just by few patients. The laterality has been included in the propensity score weights, hence has been handled in a previous step.

Please see below the code used:

```
proc mixed data=ds3 method=reml;

class USUBJID ARM AVISITn SEX MUTCD;

model CHG = ARM AVISITn SEX MUTCD AAGE BLTFON BASE ARM*AVISITn
BASE*AVISITn /ddfm=kr CL;

repeated AVISITn / subject=USUBJID type=un;

lsmeans ARM ARM*AVISITn / diff CL;

WEIGHT _ATEWgt_;

      Run;
```

Please refer to https://support.sas.com/documentation/onlinedoc/stat/141/mixed.pdf for details on procedure and references for the applied theory.[6] In particular, see on page 6079, LSMEANS Statement Section, details how the LS-mean and the standard errors for the LS-means are computed (Figure 1).

We are not able to reproduce this computation manually. It involves multiple steps of matrix operations and cannot be separated by timepoint. The MMRM is a global model in which all the components, their variability and covariability, intra subjects and between subject correlation are taken simultaneously into account.

Figure 1: Page 6079 of the PROC MIXED SAS manual[6]

LSMEANS Statement

LSMEANS *fixed-effects* < / *options* > ;

The LSMEANS statement computes least squares means (LS-means) of fixed effects. As in the GLM procedure, LS-means are *predicted population margins*—that is, they estimate the marginal means over a balanced population. In a sense, LS-means are to unbalanced designs as class and subclass arithmetic means are to balanced designs. The **L** matrix constructed to compute them is the same as the **L** matrix formed in PROC GLM; however, the standard errors are adjusted for the covariance parameters in the model.

Each LS-mean is computed as $\mathbf{L}\widehat{\boldsymbol{\beta}}$, where **L** is the coefficient matrix associated with the least squares mean and $\widehat{\boldsymbol{\beta}}$ is the estimate of the fixed-effects parameter vector (see the section "Estimating Fixed and Random Effects in the Mixed Model" on page 6133). The approximate standard errors for the LS-mean is computed as the square root of $\mathbf{L}(\mathbf{X}'\widehat{\mathbf{V}}^{-1}\mathbf{X})^{-}\mathbf{L}'$.

In addition to the mixed procedure described above and presented in Table 11 (using the observed values only), imputation methods have been used as described in the SAP (Section 7.1.2). Table 12 of the Statistical Analysis Report presents the results using aMAR imputation, while Tables 13 presents the results using aMNAR approach).

Both Table 12 and 13 Statistical Analysis Report present the results obtained with the 3 steps approach used:

1. All the missing data are imputed *m* times

2. Exactly the same mixed model applied for Table 11 is applied to each of the *m* complete datasets from point 1.

3. Results are merged applying PROC MIANALYZE procedure. Please refer to https://support.sas.com/documentation/onlinedoc/stat/131/mianalyze.pdf for details on procedure and references for the applied theory.[7]

To allow a prompt reply to this clarification question inclusive of examples, we have reduced the number of imputations from 50 to 10 (this reduced the computational time needed to run our programs) hence the results shown here do not exactly match the results contained in Table 12.

1. Example calculation

The following response reports the outputs from SAS.

For Table 11 of the Statistical Analysis Report, the mixed model for repeated measures gave the following results in terms of least squares means and difference in least squares means. This extract is also contained in OUTPUT_14_MMRM_WEIGHTED (Page 15) of the Statistical Analysis Report (B).

Figure 2: MMRM Procedure Output for Table 11of the Statistical Analysis Report – Observed data only

Abbreviations: MMRM – Mixed Model Repeated Measure

Figure 2 is made of two table of results: The first table is reporting results for the Least Squares Means (LSMEANS) for Idebenone and SOC at each timepoint. We have highlighted here the result for timepoint at 12 Months as an example. The second table is reporting the results for the difference in LSMEANS. For the difference in LSMEANS information requested on DF, t-Value, p-value are also present.

The results contained in Table 12 and Table 13 of the Statistical Analysis Report are derived applying the same mixed model for repeated measures to each of the imputed complete dataset, as per the procedure described in Section 7.1.2 of the Statistical Analysis Plan. Figure 3 shows an example from one of these *m* imputed

datasets for the MI MAR approach (results shown in Table 12 of the Statistical Analysis Report).

Figure 3: MMRM Procedure Output for Table 12 of the Statistical Analysis Report – Data of one of the imputed datasets based on MI MAR

Abbreviations: MAR – Missing At Random; MMRM – Mixed Model Repeated Measure; MI – Multiple Imputation

As stated above, this model has been run on *m* different imputed outputs. Figure 4 to Figure 6 contain the results obtained for each of the 10 imputed datasets at 12 months in terms of LSEMANS; Figure 4 for Idebenone, Figure 5 for SOC and Figure 6 for the difference in LSEMANS.

Figure 4: LSMEANS Estimates of the 10 imputed datasets for Idebenone

Figure 5: LSMEANS Estimates of the 10 imputed datasets for SoC

Figure 6: Difference in LSMEANS Estimates of the 10 imputed datasets

Results contained in Figure 4 to Figure 6 have then been put together using a PROC MIANALYZE approach. Figure 7 to Figure 9 are the results of the PROC MIANALIZE procedure applied to each of the above datasets.

Figure 7: MIANALYZE Procedure for LSMEANS Estimates of the 10 imputed datasets for Idebenone

Figure 8: MIANALYZE Procedure LSMEANS Estimates of the 10 imputed datasets for SoC

Figure 9: MIANALYZE Procedure Difference in LSMEANS Estimates of the 10 imputed datasets

2. Discussion

Figure 10 below is reporting the computation details needed to understand the MIANALYSE results.

Figure 10: MYANALYZE Procedure Theory[7]

Combining Inferences from Imputed Data Sets

With m imputations, m different sets of the point and variance estimates for a parameter Q can be computed. Suppose that $\hat{Q}_i$ and $\hat{W}_i$ are the point and variance estimates, respectively, from the ith imputed data set, $i = 1, 2, \ldots, m$. Then the combined point estimate for Q from multiple imputation is the average of the m complete-data estimates:

$$\overline{Q} = \frac{1}{m}\sum_{i=1}^{m}\hat{Q}_i$$

Suppose that $\overline{W}$ is the within-imputation variance, which is the average of the m complete-data estimates:

$$\overline{W} = \frac{1}{m}\sum_{i=1}^{m}\hat{W}_i$$

And suppose that B is the between-imputation variance:

$$B = \frac{1}{m-1}\sum_{i=1}^{m}(\hat{Q}_i - \overline{Q})^2$$

Then the variance estimate associated with $\overline{Q}$ is the total variance (Rubin 1987)

$$T = \overline{W} + (1 + \frac{1}{m})B$$

The statistic $(Q - \overline{Q})T^{-(1/2)}$ is approximately distributed as t with v_m degrees of freedom (Rubin 1987), where

$$v_m = (m-1)\left[1 + \frac{\overline{W}}{(1+m^{-1})B}\right]^2$$

The degrees of freedom v_m depend on m and the ratio

$$r = \frac{(1+m^{-1})B}{\overline{W}}$$

The ratio r is called the relative increase in variance due to nonresponse (Rubin 1987). When there is no missing information about Q, the values of r and B are both zero. With a large value of m or a small value of r, the degrees of freedom v_m will be large and the distribution of $(Q - \overline{Q})T^{-(1/2)}$ will be approximately normal.

As per Figure 10, the total variance of the aggregated result from MIANALYZE is derived as a sum of *Between* imputations variance and *Within* imputations variance.

For LSMEANS of Idebenone: *Between* = [redacted], *Within* = [redacted].

For LSMEANS of SoC: *Between* = [redacted], *Within* = [redacted].

For Difference in LSMEANS: *Between* = [redacted], *Within* = [redacted].

For the LSMEANS, both for Idebenone and SoC, there is a stronger component of the variance between imputations, that translates in a higher Standard Error than the Standard Error for the difference in LSMEANS. Therefore, the focus must then be moved to the reason why the LSMEANs vary more than the difference in LSMEANs among the m-imputed datasets.

The MI is a step-by-step approach. In imputing a missing data, a value is randomly picked from a distribution based on all the covariates included in the model, i.e. as per Statistical Analysis Plan Section 7.1.2) gender, age at onset, time from onset at baseline, baseline best BCVA, LHON mtDNA mutation. Therefore, the imputed points have a huge variability, mainly inherited from the variability of the endpoint within the covariates. The high *between* variance component of the LSMEANS is expected to be driven by the variability of the many factors on which the imputation is dependent. Being the LSMEANS DIFFERENCE a linear combination of the same covariates for each of the LSMEANS, their variability is elided, obtaining less variability.

By contrast the Markov Chain Monte Carlo imputation (first step in the applied MI as per Statistical Analysis Plan 7.1.2) and the monotone regression imputation (second step in the applied MI as per Statistical Analysis Plan 7.1.2), the implicit imputation done by the MMRM to generate Table 12 of the Statistical Analysis Report, considers all the data globally, i.e., all the data points are taken into account in their joined distribution, as well as the covariance of all the joined distribution of the covariates and of the endpoint through the collected timepoints. This generates values that are more stable among the implicit imputations, thus resulting in a lower variance.

(A9 follow-up) In addition to question A9, please provide tables of baseline characteristics for the weighted and the unweighted ITT analysis populations including variance data (standard deviation, median/range) for: analysis age (at first onset), time from first onset at baseline, baseline best visual improvement (LogMar).

The baseline characteristics for the unweighted ITT population are presented in Section 5.2, Table 10 of the Statistical Analysis Report, provided to the EAG as part of the company's response to the DGC.

As detailed in the company's response to A6, the PS model has been run on the baseline characteristics of three different sets of ITT patients. The weighted baseline characteristics for SET 2 and SET 3 are provided in the Statistical Outputs (OUTPUT_13_PSMODEL_SAMPLES_WEIGHTED for SET 2 and OUTPUT_35_PSMODEL_SAMPLES_WEIGHTED_TTE for SET 3), the accompanying document to the Statistical Report.

The baseline characteristics presented in Table 1 of the company's response to the DGC are from the SET 1 weighted population.

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, the EAG requests that all scenarios are implemented as user selectable options in the CEM so that they can be combined if required. Furthermore, if the company updates its base case results following any changes, 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.

Treatment effectiveness

B1. Priority question. The company has stated that they have applied a FIRTH penalised maximum likelihood estimation to avoid complete separation of the data and to reduce bias. Please can the company explain how the adjustment has been applied, provide further justification for its use given sensitivity analyses are already used to explore and control for parameter uncertainty and conduct a scenario removing the FIRTH estimation.

Firth's Penalized Likelihood is a simplistic solution that can mitigate the bias caused by rare events in a data set. The '*Called by the FIRTH option in PROC LOGISTIC'* method will even converge when there is complete separation in a dataset and traditional Maximum Likelihood (ML) logistic regression cannot be run, like in some of our transition probabilities. The implementation of the Firth method has advantages as compared to other potential methods, including Fisher's Exact test, traditional ML logistic regression, and Exact logistic regression.[8]

B2. Priority question. Please provide a scenario in which transition probabilities (TPs) are applied for up to 48 months, using the MNAR and MAR, weighted and logistic models.

The company maintains that the decision to use transition probabilities up to month 36 from the integrated analysis and assuming no further movement after 36 months was appropriate. This approach was taken due to limitations in the data from months 42 and 48, primarily driven by small sample sizes. As shown in Tables 5 and 7 of the company's DGC response document only [redacted] observations were recorded at month 42 for both idebenone and SoC arms, which reflects a natural limitation of the data.

Furthermore, this approach was validated with clinical experts as detailed in the company's response to issue 3 of the DGC response document, where experts agreed with the company's approach in assuming patients do not transition after month 36 due to the limitations in the data. The clinicians noted they would still expect to see patients move health states after month 36, however, given the limitations in the data past month 36 and the strength of the integrated analysis up to 36 months, all clinicians agreed that it was appropriate to assume no further movement after 36 months. (Please refer to Appendix D of the company's DGC response for more details on the clinician validation).[9]

However, in order to aid the EAG in their analysis, the company has conducted a scenario that applies transition probabilities up to 48 months for the four integrated analysis datasets requested; logistic models and weighted observed models under both MNAR and MAR assumptions. Transition probabilities were derived from the integrated analysis in the same manner as detailed in the company's response to issue 1 in the DGC response document. Similar to the company's base case analysis, patients are assumed to remain in the same health state from month 48 over the remaining time horizon of the model.

As shown in Table 3, the scenario results of applying transition probabilities up to 48 months are comparable to the company's base case results, where transition probabilities are only applied up to 36 months. This demonstrates the completeness and robustness of the company's model when modelling the long-term impact of idebenone. The results from applying transition probabilities up to 48 months for each integrated analysis datasets show that the ICER varies from £29,149 to £ 31,094 using

the company's original 8-state model structure, with ICERs of three out of four integrated analysis datasets falling below a WTP threshold of £30,000 per QALY and the remaining ICER only being £1,000 above the WTP threshold of £30,000 per QALY. These scenarios provide reassurances that the company's model structure is sufficiently robust to extended long-term modelling and provide evidence that assuming no further movement after 36 months accurately reflects the long-term efficacy of idebenone and SoC.

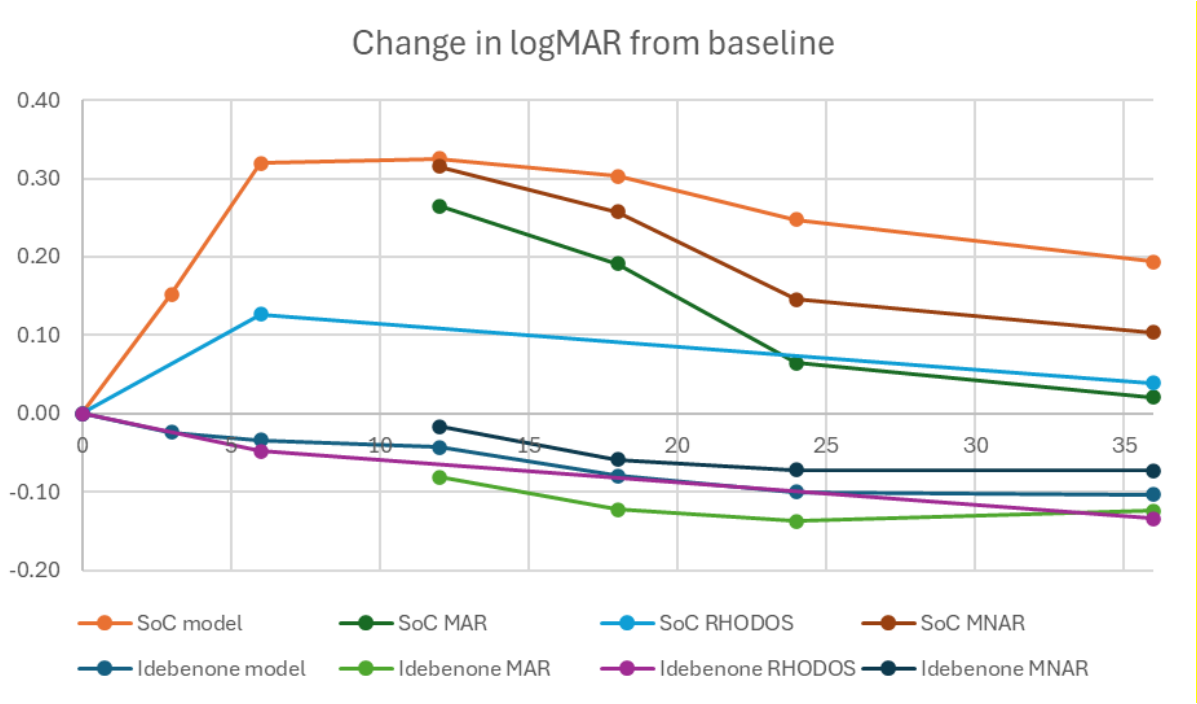
Table 3. Deterministic scenario results applying transition probabilities up to month 48 (PAS price)

Clinical inputs - Integrated data	Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Base case (Logistic model, MAR, TPs up to 36 months)	**SoC**	[redacted]	[redacted]	**-**	**-**	**-**
	Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	**28,451**
Scenarios: TPs up to month 48 (in both treatment arms)						
Logistic model, MAR	SoC	[redacted]	[redacted]	-	-	-
	Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	29,387
Logistic model, MNAR	SoC	[redacted]	[redacted]	-	-	-
	Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	29,405
Weighted observed, MAR	SoC	[redacted]	[redacted]	-	-	-
	Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	29,149
Weighted observed, MNAR	SoC	[redacted]	[redacted]	-	-	-
	Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	31,094

Abbreviations: ICER – Incremental cost-effectiveness ratio; MAR – Missing at random; MNAR – Missing not at

B3. Priority question. Please comment on how well the economic model reflects the company's integrated analyses given Figure 1 below which shows how much the model overestimates the deterioration of logMAR compared to the integrated analyses. Similarly, please explain the difference in change in logMAR from baseline to six months between SoC RHODOS patients (+0.127) and those in the model (+0.31) given the use of RHODOS to derive transition probabilities to six months.

Figure 11



The company would like to highlight that the EAG's plot in Figure 1 uses the change in logMAR from the weighted not imputed data from the Statistical Analysis Report (Table 11) which is not using the MAR MI or MNAR MI assumption. As described in the company's response to Question A1, the MMRM was first run using a traditional approach with no imputation with the outcomes presented in Table 11 of the Statistical Analysis Report. The MMRM analysis was then run using a MAR and MNAR MI imputation approach with the outcomes presented in Table 12 and Table 13 of the Statistical Analysis Report, respectively. The logistic MAR and weighted observed MAR transition probabilities used in the company's economic model from month 6 onwards align with the data presented in Table 12 of the Statistical Analysis Report.

Similarly, the logistic MNAR and weighted observed MNAR transition probabilities align with Table 13 from the Statistical Analysis Report. Therefore, the company consider it more accurate to compare the model outcomes to the outcomes of the MMRM analysis using the MAR and MNAR MI approaches (Table 12 and Table 13 from the Statistical Analysis Report, respectively). Please see

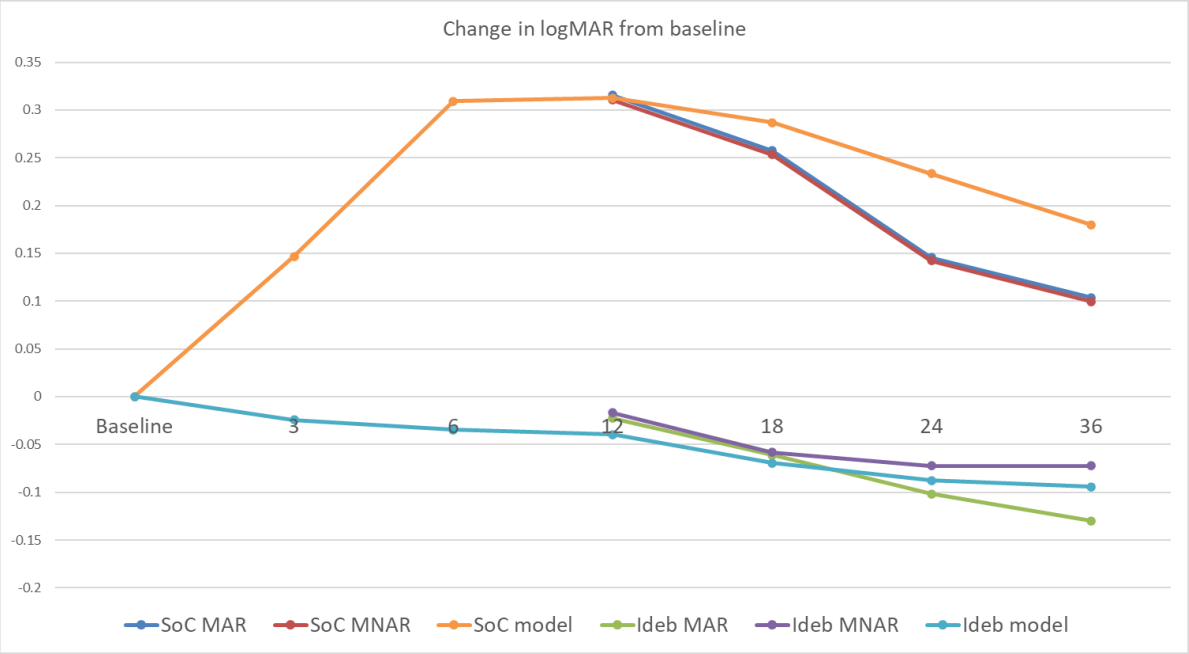
Table 4 and Figure 12 for the comparisons of the model outputs using the company's base-case assumptions and the outputs from the MMRM analysis using MAR and MNAR MI approaches.

Table 4: Change in logMAR from baseline across model outputs and the integrated analysis outputs

Timepoint	Idebenone			SoC		
	Economic model (logistic, MAR)*	Integrated analysis (MMRM, MAR)	Integrated analysis (MMRM, MNAR)	Economic model (logistic, MAR)*	Integrated analysis (MMRM, MAR)	Integrated analysis (MMRM, MNAR)
Month 6	[redacted]	N/A	N/A	[redacted]	N/A	N/A
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Under the company's base-case assumptions
Abbreviations: MAR – Missing at random; MNAR – Missing not at random

Figure 12: Change in logMAR comparison of model outputs and the integrated analysis outputs using Table 12 and Table 13 of the Statistical Analysis Report



*Model outputs are generated using the company's base-case assumptions (transition probabilities under the logistic model, MAR assumption)
Abbreviations: MAR – Missing at random; MNAR – Missing not at random

Based on the values presented in

Table 4 and Figure 12, the outputs from the economic model closely align to the outputs from the integrated analysis (MAR and MNAR approaches). In the SoC arm at month 36, there is less than logMAR [redacted] difference between the model outputs and the outputs of the integrated analysis, which clinicians have previously stated to not be clinically significant. Furthermore, in the idebenone arm at month 36, there is a difference of ~logMAR [redacted] between the model outputs and the outputs of the integrated analysis, which is equivalent to only around 2 letters. Therefore, such consistent results indicate that the economic model accurately reflects the long-term treatment effect of idebenone and SoC as validated by the outcomes of the integrated analysis.

The difference in change in logMAR from baseline to six months in the SoC arm, between the SoC model (+0.31) and the SoC RHODOS patients (+0.127) is due to differences in baseline health state distribution. The economic model uses a pooled baseline health state distribution for both treatment arms, as derived from the integrated analysis, rather than health state distribution based on RHODOS only. When using the RHODOS only health state distribution the difference in change in

logMAR from baseline to 6 months in the SoC arm for the economic model is ~[redacted] which is more closely aligned with the SoC RHODOS observation.

The company maintain that using the pooled baseline health state distribution from the integrated analysis is the most appropriate baseline health state distribution. A pooled baseline distribution takes into account all of the available clinical data (including RHODOS) and the use of EAP and CaRS studies means it is reflective of real-world clinical practice. For instance, out of the 111 patients enrolled in the EAP study, [redacted]% of patients were based in Germany, [redacted]% in the UK, [redacted]% in Australia/New Zealand, [redacted]% in Poland, Sweden, Spain, Turkey and Switzerland and [redacted]% were based in the USA. Similarly, out of the 219 patients for who data was collected on as part of the CaRS study, 26% of patients were based in Germany, 18% in Poland, 14% in Belgium, 13% in France, 9% in Italy, 11% in the Netherlands and 9.1% in the UK. Therefore, given that the majority of patients included in studies considered in the integrated analysis were based in Europe, the pooled baseline distribution from this analysis is considered generalisable to the UK clinical practice.

Furthermore, the choice of a pooled baseline distribution from the integrated analysis was validated by UK clinicians during the clinician validation interview conducted on October 17th, 2024, with one clinician stating that the baseline distribution from the integrated analysis cannot be disputed given that it is based on such a large dataset (Please see Appendix D of the DCG for further details on the clinician validation).[9]

At every timepoint of the model, the best possible data sources are used to ensure that the clinical benefit of idebenone is accurately captured compared to SoC. This means using the pooled baseline distribution from the integrated analysis and the only head-to-head RCT for idebenone (RHODOS) from baseline to month 6 and then supplementing the long-term modelling with data from the integrated analysis from month 6 onwards. However, using multiple data sources means that the results from the economic model may not be fully aligned with results from a single source i.e RHODOS at 6 months, or the integrated analysis in later timepoints. Despite this, the company consider the differences in the outputs of the model compared to the outputs from integrated analysis to be minor (as demonstrated in

Table 4 and Figure 12) and maintain that the economic model accurately reflects the clinical evidence as well as the integrated analysis.

B4. Priority question. The EAG considers that it is highly inappropriate to use RHODOS to calculate transition probabilities for the first six months of the model given the treatment effects are highly uncertain (due to small number of observations) and the uncertainty is not appropriately accounted for in the model.

Using RHODOS, the transition probabilities for the health states with the lowest visual acuity for SoC patients from month 0 to 3 are informed using only four observations and provide probabilities of 100% even under probabilistic conditions. This in turn leads to health state occupancy being zero for certain health states which is clinically implausible. As a scenario please use the integrated analyses (the MNAR and MAR, weighted and logistic models) to inform SoC and idebenone transition probabilities up to 12 months. Please additionally provide the equivalent of Figure 1, showing how mean LogMAR changes over time when using only the MMRM models to inform transition probabilities.

The company would like to highlight that RHODOS is the only head-to-head RCT that directly compares idebenone patients to SoC patients, making it a robust evidence base for assessing the clinical value of idebenone compared to SoC. As highlighted by the NICE manual, there is "*a strong preference for high-quality RCTs*" as part of NICE technology appraisals.[10] Therefore, RHODOS is the strongest and most appropriate data source for inclusion in this CEA and the company considers it suitable in informing the transition probabilities from baseline to month 6 in the economic model.

Furthermore, the company would like to highlight that within the EAG's most recent report, it was concluded that the "*EAG considers that using the treatment effect from RHODOS to inform the idebenone and SoC treatment effect for the first six months of the model is appropriate"* (ID547 idebenone committee papers).

Although the duration of RHODOS is limited to 6 months, the company has supplemented the long-term modelling of idebenone and SoC using the integrated analysis from 6 months onwards to reduce any uncertainty in the long-term relative treatment effect. The integration of the RHODOS data with the data from various other LHON studies, including a natural history study (CaRS), a real-world evidence study

(EAP) and a single-arm trial (LEROS), is not appropriate due to the methodological differences of the types of studies that would introduce bias into the outcomes.

The company acknowledges that there are a limited number of patients included in the RHODOS trial, however, this is due to the ultra-rarity of LHON and is a common limitation in all rare diseases. The small patient numbers inevitably mean that transition probabilities result in 0% occupancy in some health states at very few time points.

As highlighted in the company's response to questions A3 and A4 and reported in the integrated analysis statistical report, after the onset of LHON, the disease progression is expected to be characterised by a quick deterioration until the 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. As the statistical model used to evaluate the outcomes of the integrated analysis is based on a regression model, including all the known prognostic factors, the lack of linearity means the MMRM, MI, MAR, MNAR approaches cannot be conducted on data from baseline to month 12. Hence, even if it was appropriate to combine the RHODOS RCT with the data from all other LHON studies, it is impossible for the integrated analysis to be used to inform transition probabilities from baseline to month 6. Therefore, the company has not presented this as a scenario.

B5. Priority question. The company has stated that in contrast to the previous models submitted, transition probabilities have now been made probabilistic, allowing for the uncertainty in treatment effects to be characterised. The EAG notes, however, that the method used by the company to vary transition probabilities leads to some deterministic transition probability not being captured within the probabilistic transition probabilities calculated during the normalisation stage. Additionally, the standard errors lack face validity, with the standard error [SE] for a transition probability informed from a single observation being calculated at 0.0098.

The tables below present the deterministic and normalised probabilistic idebenone transition probabilities from months 0 to 3. As shown, the probabilistic transition probabilities are highly favourable to the idebenone treatment effect with 15% more patients remaining in the <0.3logMAR health state in the first cycle compared to the deterministic values (90% compared to

75%). As previous stated, the SEs calculated are small, leading to little variation around the normalised probabilistic transition probabilities in Table 2. While not shown, the opposite is true for the SoC treatment effect. The EAG therefore considers that the underlying data informing the transition probabilities is not reflected in the probabilistic sensitivity analysis (PSA).

Table 5. Idebenone deterministic transition probabilities from months 0 to 3.

	Transition to							
Transition from	LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6-1.0	LogMAR 1.0-1.3	LogMAR 1.3-1.7	CF	HM	LP
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6 Idebenone deterministic transition probabilities from months 0 to 3.

	Transition to							
Transition from	LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6-1.0	LogMAR 1.0-1.3	LogMAR 1.3-1.7	CF	HM	LP
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 3 presents the deterministic and probabilistic means when only treatment effects are varied in the PSA. As presented the iterations are highly constrained, with the deterministic mean not being captured in the distribution of the PSA, further suggesting that the company's method for varying the treatment effects is inappropriate.

Figure 13. ICEP when only treatment effects are varied within the PSA

Please can the company explain how SEs have been calculated for the transition probabilities, given they appear to not account for the number of observations. Please also justify the company's approach to how probabilistic transition

probabilities have been derived, particularly the normalisation step, given the lack of overlap with the deterministic probabilities for some transition probabilities. Please conduct a scenario analysis which allows for the treatment effect to be varied around the deterministic values using the best-practice approach of mean +/- SE (Briggs et al. 2008)[11] as captured in RHODOS and integrated analyses.

The company would like to highlight that all transition probabilities are captured within the probabilistic analysis. However, if the transition is 0%, the SE is calculated as a 20% of the mean so will also be 0 and is therefore not varied in the PSA. Furthermore, the SE for a transition probability is not informed from a single observation. Please see below for further details.

Months 0 - 6

The transition probabilities from RHODOS were calculated based on patient-level data and patient counts, therefore, SE were not calculated for the transition from baseline to month 6.

Months 6 - 12

Similarly, the transition from month 6 to month 12 and the transitions using the weighted observed data were calculated based on observations from the integrated analysis, weighted based on stabilised inverse probability of treatment weights, and therefore no SEs are available for these transitions. In order to overcome this limitation, the Company made a simplistic assumption to take the average SE values from the month 12 to month 18 transition probabilities derived using the logistic model and use this value to vary the transitions from baseline to month 12 and the weighted observed transitions. This value was calculated as [redacted].

Months 12 - 36

For the transition probabilities derived using the logistic model for month 12 to month 36, SEs were derived alongside the probabilities. As reported in Section 7.4, data were imputed under a MAR or MNAR approach m times creating a m set of complete datasets. A logistic regression model was then applied to estimate the probability and SE in each of the imputed datasets and results were then merged under Rubin's rule. The SEs were then used to vary the month 12 to month 36 transition probabilities when using the integrated data from the logistic model.

Months 36+

As no further movement of patients is assumed beyond 36 months, the SE in the model is 0.

Use of the beta distribution

The Company applied the beta distribution to vary the transition probabilities in the PSA and then incorporated a normalisation step in order to ensure the total percentage in each health state equated to 100%. A beta distribution has been applied to all other probability parameters in the economic model and also allows for the SEs calculated for the transition probabilities from month 12 to month 36 (logistic model) to be directly applied in the variation of the probability matrix.

The Company would like to highlight that Briggs et al. 2012 suggest the use of the beta distribution, which is used within the model. The transition probabilities are varied with the mean +/- the SE in line with best practice as requested by the EAG.

The Company adjusted the approach with which they varied the transition probabilities in line with Equation 2 in question B23. With this adjustment, probabilistic transition probabilities are close to the determinist ones for both the idebenone and SoC arms. Please see the Company's response to Question B23 and B24 for further exploration on the Company's approach to varying the transition probabilities and the SE values applied.

B6. Priority question. Please provide the proportion of patients with logMARs according to the economic model, who contributed to the mean logMARs reported in Table 11, 12 and 13 of the integrated statistical plan report using the Table format below. E.g. 20% of SoC patients in the integrated analysis reported a logMAR between 1.3-1.7 at month 12 (this is an example and not a known proportion).

All patients who contributed to tables 11,12 and 13 of the integrated statistical plan report were included in the derivation of the transition probabilities for the economic model.

Please find the proportion of patients in each health state at given timepoints in the economic model under the company's base case assumptions i.e the logistic model MAR assumption, in Table 7 and Table 8. A half-cycle correction has been applied.

Table 7: Proportion of idebenone patients in each health state at each timepoint as derived from the company's base case cost-effectiveness analysis

Proportion of patients in each health state at given timepoints	Baseline	Month 3	Month 6	Month 12	Month 18	Month 24	Month 36
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP	[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

Table 8: Proportion of SoC patients in each health state at each timepoint as derived from the company's base case cost-effectiveness analysis

Proportion of patients in each health state at given timepoints	Baseline	Month 3	Month 6	Month 12	Month 18	Month 24	Month 36
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LP	[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

B7. Priority question. Provide the number of patient observations from the MAR models that have been used to derive the transition probabilities. For the MAR model please state what proportion of observations have been imputed across all timepoints.

As detailed in Section 7.4 of the Statistical Analysis Plan, for month 6 to month 12 transition probabilities are based on observations obtained from the integration of all studies i,e SET 1: All ITT patients with at least one assessment at 6 Months or 12 Months analysis visit, excluding those enrolled in RHODOS study. No imputation was applied to the transition probability from month 6 to month 12. This resulted in a total of [redacted] idebenone patients and [redacted] SoC patients having been included in the month 6 to month 12 transition probabilities.

For month 12 onwards, transition probabilities are based on observations obtained from SET 2: All ITT patients with at least one assessment on or after 12 Months analysis visit. In this analysis, assessments in the RHODOS follow-up were included for the SoC arm only. Idebenone patients are not included since they were no longer on treatment. This resulted in a total of [redacted] idebenone patients and [redacted] SoC

patients having been included in the month 12 to month 36 transition probabilities. Please see the company's response to Questions A3b) for the number of patients with at least one assessment at each timepoint by treatment group in the SET 2 population and for a detailed description on the proportion of observations that have been imputed across timepoints.

B8. In clarification question A3, the EAG has requested the company to conduct an analysis using the matched patients baseline best BCVA and final follow-up visit without imputation. Please can the company conduct a scenario using this analysis to derive transition probabilities.

See reply to question A3.c

As highlighted in the company's response to question A3, the integrated LHON studies have considerable differences in the follow-up of patients. Considering the final follow-up visits for all patients, would be comparing assessments from a visit at 12 months for one patient with the assessment of a visit at 36 months for another patient. This will introduce substantial variability in the results, and they would lack any clinically meaningful interpretation for assessing the clinical value of idebenone compared to SoC. Therefore, the company does not consider this scenario clinically accurate or appropriate and it has not been conducted.

B9. The company has stated their preference of separately assessing the 6-month analysis visits from the 12-month analysis visits to avoid the assumption of linearity, however, the company has assumed linearity in the model by assuming all patients will have unchanged logMAR every other cycle in the model (between cycles 2 to 3, 4 to 5, 6 to 7, 8 to 9, etc.). As a scenario, please conduct a scenario which groups the 6-month visits with the 12-month visits.

To reiterate the company's point in the response to questions A3 and B4, after the onset of LHON, the disease progression is expected to be characterised by a quick deterioration until the nadir followed by a slow stabilization with some cases of spontaneous improvement. For this reason, the assumption of linearity cannot be made in the first months after baseline and hence, all the assessments including up until the 6 month analysis visit have been analysed separately from the assessments included in the 12 month analysis visit onwards in the integrated analysis.

The company do not assume any linearity in the economic model. The functionality of the model is set up to adopt 3-month cycles, as stated in the company submission, and the company previously derived the transition probabilities every 3 months when using the RHODOS and EAP patient level data. The integrated analysis has been conducted using 6-month analysis visits from month 6 onwards. Therefore, in order to add the transition probabilities from the integrated analysis into the economic model without changing the model structure, the company have applied each 6-month transition probability from the integrated analysis in every other 3-month cycle in the model, with the assumption that patients will stay in the same health states for the first 3-month cycle. A similar approach was conducted in the company's previous scenario when using LEROS transition probabilities and does not assume linearity.

Utilities

B10. Priority question. Please explain how health state utility SEs have been calculated given they do not change according to the source of utilities. The EAG additionally notes that the utilities derived by Lawrence et al. have confidence intervals different to those assumed in the model.

Health state	Lawrence et al. (2023) - HUI-3	SE	Brown et al. (1999)	SE
Patient utility - logMAR <0.3	0.84	0.12	0.84	0.12
Patient utility - logMAR 0.3-0.6	0.51	0.12	0.77	0.12
Patient utility - logMAR 0.6-1.0	0.44	0.12	0.67	0.12
Patient utility - logMAR 1.0-1.3	0.35	0.12	0.63	0.12
Patient utility - logMAR 1.3-1.7	0.33	0.12	0.54	0.12
Patient utility - CF	0.21	0.12	0.52	0.12
Patient utility - HM	0.19	0.12	0.35	0.12

Patient utility - LP	0.18	0.12	0.35	0.12

The company would like to thank the EAG for pointing out the error in the calculation of SE for the utility values. The company has corrected this in the model and updated the SE to be equal to 20% of the mean value, in line with the approach used to calculate the SE of most other parameters in the economic model. A default of 20% of the mean value is used as the SE in the economic model when the SEs are not readily available from the source. Although the upper and lower bound confidence intervals are plotted as part of the figures included in the Lawrence et al. (2023) publication, the actual values are not given, therefore, a default of 20% of the mean value has been taken as the SE in the economic model and used to calculate the intervals.[12] Hence why the utilities derived by Lawrence et al. (2023) have confidence intervals different to those assumed in the model.[12] The updated SEs and upper and lower confidence intervals for the company base case source of HUI-3 utility values from Lawrence et al. (2023) are presented in Table 9.[12]

Table 9: Updated health state utility values and standard errors.

Health state	Lawrence et al. (2023) - HUI-3	SE	Patient utility lower confidence interval	Patient utility upper confidence interval
LogMAR <0.3	0.84	0.17	0.40	1.00
LogMAR 0.3-0.6	0.51	0.10	0.31	0.71
LogMAR 0.6-1.0	0.44	0.09	0.27	0.61
LogMAR 1.0-1.3	0.35	0.07	0.22	0.49
LogMAR 1.3-1.7	0.33	0.07	0.20	0.46
CF	0.21	0.04	0.13	0.30
HM	0.19	0.04	0.12	0.27
LP	0.18	0.04	0.12	0.26

Abbreviations: CF – Counting fingers; HM – Hand motion; HUI – Health utilities index; LogMAR – Logarithm of the minimum angle of resolution; LP – Light perception; SE – Standard error

B11. Priority question. Due to the wide confidence intervals of the health state utility values, under probabilistic conditions those with worse visual acuities can often have better health-related quality of life than those with better visual

acuities as presented in Table 10 below. Please conduct a scenario where health care utility values are fixed in the PSA.

Table 10. Health state utility values and standard errors.

Health state	Lawrence et al. (2023) - HUI-3	SE	Patient utility lower confidence interval	Patient utility upper confidence interval
LogMAR <0.3	0.84	0.12	0.55	0.99
LogMAR 0.3-0.6	0.51	0.12	0.28	0.74
LogMAR 0.6-1.0	0.44	0.12	0.21	0.67
LogMAR 1.0-1.3	0.35	0.12	0.14	0.59
LogMAR 1.3-1.7	0.33	0.12	0.12	0.58
CF	0.21	0.12	0.04	0.48
HM	0.19	0.12	0.02	0.47
LP	0.18	0.12	0.02	0.46

As provided in the response to B10 above, the company have corrected the error in the calculation of the SE values for the utility values. However, in order to address the EAG's uncertainty in the wide confidence intervals, the company has also run the PSA with fixed utility values. Please find the results of the 10,000 iterations PSA using the company's base-case settings and fixed utility values in Table 11. The current ICER of £23,687, with the fixed utility values, shows minimal impact from the original PSA ICER of £23,879.

Table 11: Base-case PSA results with fixed utility values (PAS price)*

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
SoC	[redacted]	[redacted]	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	23,687

* As this was part of the responses submitted on Monday, December 2nd, this PSA was run without the correction presented in equation 2 of question B23
Abbreviations: ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life-years; SoC – Standard of care

B12. Priority question. The EAG notes that the SE for the carer disutility is the same as has been assumed for the health state utilities (0.12), in addition to being three times that of the mean disutility itself (0.04). The EAG additionally notes that different carer disutilities are applied to the different health states under probabilistic conditions, and as the SE is so large, the carer disutility can reduce the health state utility to 0 under probabilistic conditions. As such, while the EAG considers that carer disutility should be included in the model, its inclusion introduces significant uncertainty which is not adequately accounted for. Please can the company provide the source of the carer disutility SE, and conduct a scenario where care disutility is fixed in the PSA.

The company would like to thank the EAG for pointing out the error in the calculation of SE for the disutility values. As above, the company has corrected this in the model and updated the SE to be equal to 20% of the mean value given that the SE of the values is not readily available from the source.[13] Furthermore, in order to address the EAG's uncertainty in the varying of the caregiver disutility, the company has also ran the PSA with fixed disutility values. Please find the results of the PSA using the company's base-case settings and fixed disutility values in Table 12. The updated PSA ICER remains well below the £30,000 WTP threshold and shows minimal deviation from the original PSA ICER result of £23,379.

Table 12: Base-case PSA results with fixed caregiver disutility values (PAS price)*

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
SoC	[redacted]	[redacted]	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	24,391

* As this was part of the responses submitted on Monday, December 2nd, this PSA was run without the correction presented in equation 2 of question B23
Abbreviations: ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life-years; SoC – Standard of care

B13. Priority question. The company has stated their preference for a carer disutility to be applied for all patients with a 1>logMAR, who are not in residential care. The EAG's clinical experts stated that after a number of years, patients who go blind will eventually have a high level of autonomy after

adapting to their loss of sight. Therefore, please conduct a scenario analysis applying the carer disutility for a fixed amount of time e.g. 3, 4 or 5 years, for patients with 1>logMAR who are not in residential care.

LHON is a severely debilitating condition characterised by rapid vision loss of VA with over 50% of eyes deteriorating to logMAR above 1.0 within one week of disease onset).[14] It is a condition which significantly affects patients' quality of life, disrupting their education, careers, and family life as it typically occurs in the second and third decades of life[15], at a time when patients are expected to be beginning their careers or starting a family.[16–19] This suggests that patients with LHON will require a substantial amount of long-term support from caregivers to adjust to a new way of living, and thus it is expected to impact the quality of life of caregivers in the long-term. This is further supported by the EAG's clinical experts which "*explained that most people with LHON need constant support from family members and carers*" (Section 3.15, DGC[20]).

The timeline for adaptation to blindness can vary widely based on individual circumstances, the ease of access to rehabilitation services, the severity of visual impairment, the duration of vision loss progression and the patient's mental well-being. While autonomy may improve with rehabilitation, many patients may continue to require intermittent or regular support for tasks that require visual inputs, such as travel, recreational activities and accessing digital information.

Caregiver burden may also persist despite patients gaining some independence as caregivers often remain involved in supporting complex tasks such as providing emotional, travel and social support and financial management, especially since LHON primarily affects young adults. This sustained burden and the complexities of blindness and its long-term effects on both the patients and caregivers should not be underestimated when modelling the caregiver's utility impact. Therefore, the company maintains that the caregiver disutility of 0.04 should be applied across the lifetime horizon of the model and not just a limited amount of time. 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.[13]

However, to address the EAG's request for "applying the carer disutility for a fixed amount of time", the company has tested scenarios involving applying the caregiver

disutility of 0.04 for a limited amount of time of 5 and 10 years, followed by 0.02 caregiver disutility applied for the remainder of the time horizon, respectively. This approach is considered more realistic than removing the disutility altogether after a short period of 3, 4, or 5 years. While LHON patients may adapt to blindness over time, they are still likely to require some level of ongoing support. Halving the disutility acknowledges this adaptation while reflecting the continued need for assistance, aligning with the clinical and patient experts (see above).[20]

The scenario analysis for applying caregiver disutility of 0.04 for 5 years and 10 years and then a caregiver disutility of 0.02 for the remainder of the time horizon is presented in Table 13.

Table 13. Deterministic scenario results applying reduced caregiver disutility at selected time points (PAS price)

Scenario	Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Base case (Apply a disutility of 0.04 over a lifetime)	SoC	[redacted]	[redacted]	-	-	-
	Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	28,451
Scenarios: Apply 0.04 caregiver disutility for given number of years, then apply a caregiver disutility of 0.02 for the remainder of the time horizon						
5 years (then 0.02 caregiver disutility)	SoC	[redacted]	[redacted]	-	-	-
	Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	29,429
10 years (then 0.02 caregiver disutility)	SoC	[redacted]	[redacted]	-	-	-
	Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	29,216

Abbreviations: ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life-years; SoC – Standard of care

The scenario presents a minimal ICER increase of £978 from £28,451 to £29,429 for the 5 years scenario and an increase of £765, from £28,451 to £29,216 for the 10 years scenario.

Similar results of base case and scenarios around caregiver disutilities demonstrate that the company's model captures robustly impact of carer disutilities. Furthermore, even under the most conservative assumption of applying a reduced caregiver disutility from 5 years, the respective ICER still remains under £30,000 per QALY.

Health care resource use

B14. Priority question. Please can the company provide further explanation as to how the proportions of patients assumed to be hospitalised and require outpatient care have been informed. Please justify the proportions assumed for outpatient care given that providing low vision aids is unlikely to be a recurring cost and rehabilitation is unlikely to be required in the long term, as logMAR is assumed to be constant from three years onwards. As a scenario, please assume outpatient care is only required for up to three years from the start of treatment.

The proportion of patients assumed to be hospitalised and require outpatient care have been informed using midpoint estimates between the company's KOL survey and Meads et al. (2003) for each health state.[21] The values from the company's KOL survey were populated by three international ophthalmologists and later validated by five UK clinical experts as part of this appraisal (CS, Appendix N).[22]

As part of the company's response to the DGC, the company's updated base-case applies outpatient care costs as a one-off cost to patients across all health states, as aligned with the setting in the EAG's base-case at ACM1.[20] This assumption therefore does not assume that outpatient care costs will be a recurring costs or required in the long-term. Therefore, given this misunderstanding, the company do not think a scenario assuming that outpatient care costs are only applied for up to three years is needed. Furthermore, the model includes functionality to include outpatient costs across the lifetime time horizon which reduces the ICER to £27,968, suggesting that the requested scenario will have minimal impact on the current base-case ICER of £28,451.

B15. Priority question. Given the company's clinical experts have stated, "*The reason for the increase [in outpatient care] was the fact that with no treatment available there is little value to be gained from a clinic visit, therefore with the introduction of idebenone an increase is to be expected***", please discuss if SoC patients should be assumed to require the same frequency of outpatient visits given there is little value to be gained. Please conduct a scenario analysis exploring SoC patients requiring a reduced frequency of outpatient care and no outpatient care.**

As described above, the company's updated base case analysis in response to the DGC assumes outpatient costs are applied as a one-off cost to patients across all

health states in both the idebenone and SoC arms, aligning with the EAG's base-case assumption. This is an update from the company's original assumption that outpatient care costs should be applied across the lifetime time horizon at ACM1.

In order to aid the EAG in their analysis, the company has conducted the requested scenarios in which SoC patients receive no outpatient care or a simple reduction to 50% of the total outpatient care costs they received in the base case.

The deterministic scenario results for applying no outpatient care and a reduced outpatient care of 50% for idebenone vs SoC are presented in Table 14 and Table 15, respectively. The scenario presents a minimal ICER increase of £110 from £28,451 to £28,561 for the no outpatient care in the SoC arm scenario and an increase of £55, from £28,451 to £28,506 for the 50% outpatient care costs in the SoC arm scenario. This highlights that the impact on the ICER is insignificant and that the current base case reflects the existing SoC.

Table 14: Deterministic scenario results applying no outpatient care costs for SoC patients (PAS price)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
SoC	[redacted]	[redacted]	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	28,561

Abbreviations: ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life-years; SoC – Standard of care

Table 15: Deterministic scenario results applying 50% outpatient care costs for SoC patients (PAS price)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
SoC	[redacted]	[redacted]	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	28,506

Abbreviations: ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life-years; SoC – Standard of care

B16. Priority question. Please justify the assumption that patients will require outpatient care given they will also be receiving frequent ophthalmologist visits who would provide the low vision aids and rehabilitation.

The assumption that patients will require outpatient care is based on the resource use in a paper by Meads et al.[21] In this paper, costs associated with low vision aid and rehabilitation were identified which are included under outpatient care within the economic model. In Meads et al., these are defined as the following:

- The low vision aid cost was an assessment of hospital eye service prescription forms in a district general hospital.
- The cost of low vision rehabilitation is from a cost per care episode of a health authority community occupational therapist.

The outpatient cost covers a variety of costs outside of ophthalmologist visits and therefore is included as a separate cost category within the economic model. It is assumed that an ophthalmologist specialist would not have time within a visit to discuss with the patients low vision aids or rehabilitation in the same way an occupational therapist would.

Furthermore, given that outpatient care costs are applied as a one-off cost, the addition of the outpatient care cost is minimal on top of the ophthalmologist visits included within the model. The company remains confident that the additional services included in the outpatient care costs are important to capture the full range of costs for patients with LHON in the model and the impact on the ICER is minimal.

B17. Priority question. The EAG notes that health state costs have been applied in the model as a product of health care resource use and their frequencies. However in the PSA, health state costs have been calculated while accounting for the SE of the resource cost, the SE of the frequency of use per cycle and then also the SE of the total cost per cycle, all of which utilise an assumed SE of 20% under the company's base case assumptions. Given that the costs and frequency uncertainty have already been accounted for, the EAG considers it inappropriate to further adjust health resource costs using an additional

assumed SE. As such, please conduct a scenario in which only the SE of the cost and frequency of healthcare resource use are accounted for in the PSA.

The company would like to thank the EAG for identifying the double counting of the uncertainty captured in the updated PSA functionality. The company have added a scenario in which only the SE of the cost and frequency of healthcare resource use are accounted for in the PSA. The updated outcomes of the PSA ran with this scenario are presented in Table 16.

Table 16: Probabilistic scenario results varying only the cost and frequency of HCRU, company base-case (PAS price)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
SoC	[redacted]	[redacted]	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	24,334

Abbreviations: ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life-years; SoC – Standard of care

B18. Priority question. Please justify the approach of assuming a SE of 20% for all parameters where SE is unknown given this can have disproportionate effects on high-cost resources such as residential care, whose lower and upper confidence intervals are estimated as £49,000 and £107,000 given a mean of £75,000.

Using a SE of 20% for all parameters where the SE is unknown is a standard modelling practice. There are no guidelines within the NICE manual which specify a preferred value for calculating the SE when the SE is unknown. The company would like to note that within HST11 a SE of 15% was accepted suggesting that the company's current value of 20% is a conservative assumption. To aid in the EAG's analyses, the company has provided a scenario using an SE of 15% in line with HST 11. The base-case results of the PSA using a SE of 15% are presented in Table 17. As demonstrated, there is little to no difference in the PSA results compared to using a 20% SE.

Table 17: Probabilistic analysis results using a SE of 15% (PAS price)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
SoC	[redacted]	[redacted]	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	23,594

Abbreviations: ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life-years; SoC – Standard of care

Treatment discontinuation

B19. Priority question. The company's SAP states that, "*Patients who didn't experience a CRR will be censored at their last BCVA assessment.***" Please can the company confirm that these patients have been included in the integrated analyses? If not, please justify the exclusion of these patients and conduct a scenario where these patients are included in all the integrated analyses models.**

The company confirms that these patients have been included in the integrated analyses. Patients who didn't experience a CRR have been censored at their last BCVA assessment. They have been included with a NO EVENT and the time under observation computed from baseline until their last BCVA assessment, has been included in the analysis. The analysis has been performed like a traditional KM analysis, but weighted by PS score weights.

B20. Priority question. In the company's base case, in addition to treatment discontinuation (persistence), treatment compliance has also been included. Please can the company explain the difference between these proportions? The EAG additionally notes that when compliance is changed, there is a change in costs with no reciprocal change in QALYs. As such, it is assumed in the model that if idebenone patients do not discontinue treatment but also do not comply, they continue to receive the treatment effects with no treatment costs. It is the EAGs preference to therefore capture compliance within discontinuation, as such, please provide this as a scenario.

Compliance is generally defined as the degree at which a patient follows the treatment regimen and medication schedule of a drug. In RHODOS, compliance was calculated as "*a percentage by dividing the number of tablets taken by the number of days since the previous visit multiplied by six, multiplied by 100*". This is different to the definition of discontinuation, in which a patient stops treatment permanently.

In the company's base-case, compliance data is sourced from the RHODOS RCT and the clinical effectiveness of patients who do not comply is implicitly captured within the RHODOS transition probabilities used in the economic model. Based on compliance data from the RHODOS trial, 96% compliance was assumed, which means that on average patients will miss 4% of tablets (which is around 7 tablets out of 180 tablets

per month). No data were available to evaluate the influence of varying compliance rates on the treatment's efficacy. Consequently, the analysis focused solely on the impact of changing compliance rates on costs. This means that in the model 96% of idebenone acquisition costs were assumed for every patient to ensure the costs are aligned with the compliance rate found in the RHODOS trial as well as the data which informs the transition probabilities. So, for patients who do not discontinue and do not comply, the effect of non-compliance on treatment effect is already captured within RHODOS transition probabilities and the effect on cost is also captured by reducing cost of idebenone by 4% per average patient

As part of the original submission, the company explored the impact of assuming full compliance (100%) and compliance as derived from real-world evidence (87%) as costing scenarios only. The results for these scenarios were provided as part of the original company submission. The company would like to highlight a compliance of 96% from RHODOS is incredibly high for an oral drug and experts within LHON have noted that general compliance is very high within the LHON community, driven by patients' very strong desire to restore eyesight.

Given that the compliance of treatment can vary from patient to patient and given the difference in how compliance and discontinuation are defined, it is not possible to individualise compliance to incorporate it into the discontinuation analysis or the clinical effectiveness data. The data does not exist to model this. The impact of compliance and discontinuation are already reflected in the clinical data used to model transition probabilities. Therefore, it is not possible for the company to carry out the EAG's requested scenario.

However, in order to aid the EAG in their assessment, the company has explored a conservative scenario of 100% compliance for treatment costs. The scenario is applied to the company's updated base-case and presented in Table 18. As demonstrated, given the already high compliance assumed from RHODOS(96%), assuming 100% compliance has a minimal impact on the ICER.

Table 18: Deterministic results assuming 100% compliance (PAS price)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
SoC	[redacted]	[redacted]	-	-	-

Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	29,903

Abbreviations: ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life-years; SoC – Standard of care

B21. Priority question. In the draft guidance, the committee requested further scenario analysis around treatment discontinuation given there is no stopping rule in the SmPC for idebenone and patients may not want to stop treatment given treatment has led to the regaining of sight. However, the company has only provided additional scenarios around treatment discontinuation using the integrated analyses, which includes studies of a definitive length before the withdrawal of treatment, thereby limiting the maximum time on treatment. The EAG therefore considers that no additional time on treatment scenarios have been explored as requested by the committee. As such, please conduct additional scenario analyses assuming that all patients that achieve CRR at any time three years from the start of treatment will continue to receive treatment for a further length of time e.g. another one, two, five and ten years.

The Company would like to highlight that the integrated analysis does not solely include studies of a 'definite length'. In the analysis, even for the studies, such as LEROS, with fixed duration of treatment, no imputation has been done on the time on treatment. The analysis used in the economic model to inform treatment duration was performed using a KM model. This method allows to compute summaries for the time on treatment also accounting for patients who did not interrupt. These patients have been included in the analysis as censored, i.e. patients without interruption of treatment, but observed as on-treatment for a certain length of time. As described in the Company's response to the DGC, the EAP study is of retrospective, non-controlled and open-label nature and the duration of treatment was left to the opinion of the treating physician. Furthermore, at the onset of the EAP study, knowledge about LHON progression over time and the best duration of treatment was limited. Therefore, within the EAP study, there is a non-uniform duration of treatment, and a deliberately broad range of treatment duration was permitted. With the current knowledge, clinicians agreed that they will treat until stabilisation (which according to one of the clinicians would be characterised by two consecutive visits with no change in VA), or they will stop treatment if there is no response to treatment. (CS; Appendix N: Clinical validation[22]) To ensure treatment discontinuation is appropriately reflected within the economic model the company analysed 'time to indication to treatment discontinuation' that was validated by clinical experts. Clinical experts agreed that the

definition is aligned with what they would expect to use in clinical practice to decide regarding the discontinuation.[9]

The time to indication to treatment discontinuation was derived based on clinical expert opinion, with the following patients considered eligible to be discontinued from treatment:

- Patients who experience a CRR from baseline within 2 years and are then treated for additional 6 months without further CRR and until stabilisation,
- 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.

The cut-off of 2 years was informed by UK clinical experts who stated that they would expect to see patients stabilise or 'plateau' in VA around 2-3 years after the start of treatment (CS; Appendix N[22]). This was further validated in the company's clinician validation (17th October 2024; Appendix D of the company's response to the DGC), where both clinicians agree almost all patients would have stopped treatment by 36 months. One clinician stated that "*some patients would have their treatment discontinued within the first six months, as clinicians would have a better understanding of whether idebenone is effective by that point and which patients would likely stabilise*".

Figure 14: Time to indication to treatment discontinuation estimated using the integrated analysis

Based on the time to indication for treatment discontinuation variable from integrated analysis (Figure 14) it was assumed that the majority of patients would discontinue at 24 months (because they either had CRR and stabilised or have not had a response). However, there is still [redacted]% of patients at 30 months and [redacted]% of patients at 36 months with further improvement in response. The company would like to note that 36 months is not a definite cut-off to treatment, and the time to indication to treatment discontinuation KM curve used in the economic model still assumes that [redacted]% of patients are still on treatment from 36 months to 48 months. For instance, patients with further CRR after 2 years of treatment are assumed to continue the treatment, until further stabilisation.

Given that the modelling of treatment discontinuation was based on input from UK clinical experts, the company consider it highly inappropriate to conduct a scenario where it assumed that patients would stay on treatment for durations of 5, 8 or 13 years (assuming waiting 3 years for CRR and then an extra 2, 5 or 10 years). Therefore, this scenario has not been conducted.

B22. Given that the committee has requested in the draft guidance for further analysis "separating off-chart health states in the EAG model structure,

especially for counting fingers" please provide a scenario which uses the EAG's preferred model structure with the off-chart blind health states separated as presented below.

- **LogMAR less than 0.3**
- **logMAR 0.3 to 1**
- **logMAR 1 to 1.7**
- **Counting fingers**
- **Hand movement**
- **Light perception**

The company strongly considers the original 8-health state model structure to be adequately robust and clinically and economically plausible for decision-making in patients with LHON. The 8-health state model structure, based on visual acuity, captures the natural progression of the disease over time, aligning with the patient and clinical experts participating in ACM1 who agreed that the company's modelled health states capture disease severity comprehensively. This robust structure was further validated by clinical experts in the Company's recent clinician validation (17th October 2024) in which both clinicians stated that the on-chart and off-chart categories provided sufficient granularity and aligned with previous vision loss NICE health TAs.

The Company consider it highly inappropriate to merge the logMAR 0.3 to 0.6 with the logMAR 0.6 to 1.0 health states together, and similarly, the logMAR 1.0 – 1.3 and logMAR 1.3 – 1.7 health states. In the same way that the off-chart health states cannot be merged, these small differences in logMAR can have a substantial impact on a patients' quality of life. This is supported across the numerous utility studies that have been presented as a part of the company submission. In Brown et al., there is a utility difference of 0.1 between the logMAR 0.3-0.6 and logMAR 0.6-1.0 health states and a difference of 0.9 between the logMAR 1.0-1.3 and logMAR 1.3-1.7 health states.[23] This suggests a substantial difference in the quality of life between these different logMAR health states. This is further supported by the HUI-3 values presented in Lawrence et al. in which there is a utility difference of 0.07 between the logMAR 0.3-0.6 and logMAR 0.6-1.0 health states.[12] For reference, literature has demonstrated

that the minimal clinically important difference (MCID) in EQ-5D can start from 0.07 in oncology, 0.04 in PTSD and 0.03 in musculoskeletal diseases.[24]

In the original submission, the EAG and committee were concerned that the transition probabilities are populated based on a limited number of observations, however, with the integrated analysis, there is enough data to populate transition probabilities between 8 health states. Therefore, with the introduction of the integrated analysis set the company considers the 8 state model robust as it captures differences between different logMAR states, while not being limited by patient numbers. The company has also conducted numerous scenario analyses with the EAG's preferred 4-health state structure with transition probabilities derived from the integrated analyses and the results from these scenarios show that the ICERs vary from £28,345 to £32,627 using the company's revised base-case. These results are consistent with the company's 8-health states structure which show that the ICERs vary from £24,894 to £28,735. This highlights that the transition probabilities are robust to various model structures and the Company expect that this will continue when adopting various other model structures, including the structure suggested by the EAG above.

It is therefore inappropriate to group the on-chart logMAR values of 0.3-0.6 with 0.6-1.0 and logMAR 1.0-1.3 with 1.3-1.7 as grouping these logMAR values would oversimplify the nuanced severity of LHON, potentially masking significant differences in patient outcomes. Even a small change in LogMAR ranges for each health state has a substantial difference in the daily functioning of patients with LHON which translates into quality-of-life (QoL) benefits and cost savings. Therefore, the Company do not consider it clinically appropriate to conduct the requested scenario.

B23. The EAG has identified that the difference between deterministic and probabilistic probabilities as discussed in CQ B5 is in part due to the probabilistic transitions being multiplied by the deterministic transition probabilities in Step 4 (equation 1) of the probabilistic process. The EAG considers that it is inappropriate to re-multiply the probabilistic values by the deterministic and equation 2 should be used instead.

Equation 1

=IFERROR(BETAINV(RAND(),alpha,beta),0)*deterministic value

Equation 2

=IFERROR(BETAINV(RAND(),alpha,beta),0

If this is an error, please update the company base case, otherwise please justify the approach given the difference in probabilistic and deterministic transition probabilities and conduct a scenario where transition probabilities are made probabilistic using equation 2 in step 4.

The Company would like to thank the EAG for pointing this discrepancy out in the PSA. The Company has updated the base-case to vary the transition using equation 2 before applying the normalisation step. This addresses part of the EAG's concerns highlighted in Questions B5 and the probabilistic transitions from baseline to month 3 in the idebenone arm now more closely reflect the deterministic values.

The mean PSA results for the revised company base-case, are presented in Table 19. The incremental cost-effectiveness plane is provided in Figure 15 and Figure 16 presents the cost-effectiveness acceptability curve for idebenone versus SoC. As demonstrated, the base-case PSA ICER (£29,415) is now more closely aligned with the deterministic ICER (£28,451).

Table 19: Probabilistic analysis results (updated company base-case at DGC response)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Idebenone	[redacted]	[redacted]	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	29,415

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

Figure 15: Cost-effectiveness plane (updated company base-case at DGC response)

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

Figure 16: Cost-effective acceptability curve (updated company base-case at DGC response)

*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

B24. The EAG notes that the standard error of the RHODOS and weighted MRMM models have been calculated using the average SE from month 15 to 18 from the logistic MAR models. Please can the company justify this approach and conduct a scenario applying SEs derived from RHODOS and the weighted MMRM models for their respectfully derived transition probabilities at each time point.

Please see the Company's response to Question B5 for justification on how the SEs were derived for each transition.

As mentioned, SEs were not derived for the weighted observed transition probabilities from the RHODOS trial. Therefore, in order to explore the impact of the SEs of the transition probabilities on the PSA in an alternative way, the Company has conducted two scenarios, one where a SE of 20% is applied to the transition probabilities from baseline to month 12 and another where a SE of 20% is applied to all transitions. A SE of 20% is the same approach applied to all other parameters varied using a beta distribution in the economic model with no available SEs from literature (see response for question B18 for further justification of the 20% SE variation). Within the scenarios below, the equation 2 detailed in Question B23 has been applied.

The mean PSA results of the base-case whilst using a SE of 20% to vary the transition probabilities from baseline to month 12 can be found in Table 20. As demonstrated, there is minimal difference between the scenarios PSA ICER (£29,442) and the base-case PSA ICER (£29,415).

Table 20: Probabilistic analysis results using a SE of 20% for the transition probabilities from baseline to month 12 (updated company base-case at DGC response)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Idebenone	[redacted]	[redacted]	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	29,442

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

The mean PSA results of the base-case whilst using a SE of 20% to vary all transition probabilities can be found in Table 21. As demonstrated, there is minimal difference between the scenarios PSA ICER (£29,328) and the base-case PSA ICER presented in ICER (£29,415).

Table 21: Probabilistic analysis results using a SE of 20% for all transition probabilities (updated company base-case at DGC response)

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Idebenone	[redacted]	[redacted]	-	-	-
SoC	[redacted]	[redacted]	[redacted]	[redacted]	29,328

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

B25. Following from CQ B5, which raises the issue of the lack of face validity of the MRMM model SEs, please can the company provide the raw data from which the proportions of patients transitioning between health states and standard errors have been calculated (the proportions and SEs in the integrated tab). Please also provide the proportion of observations that have been imputed for each transition at each time point. With this information comment on how well the transition probability uncertainties reflect the uncertainty in the integrated analysis.

As detailed in the Company's response to Question B5, SEs were derived alongside the probabilities for the transition probabilities using the logistic model for month 12 to month 36.

Therefore, as detailed in the Company's response to Question B7, transition probabilities are based on observations obtained from SET 2: All ITT patients with at least one assessment on or after 12 Months analysis visit. In this analysis, assessments in the RHODOS follow-up were included for the SoC ARM only. Idebenone patients are not included since they were no longer on treatment. This resulted in a total of [redacted] idebenone patients and [redacted] SoC patients having been included in the month 12 to month 36 transition probabilities. Please see the company's response to Questions A3b) for the number of patients with at least one assessment at each timepoint by treatment group in the SET 2 population and for a detailed description on the proportion of observations that have been imputed across timepoints.

Given that the SEs of the transition probabilities from month 12 onwards in the Company's base-case are directly calculated using the logistic model from the integrated analysis, the transition probability uncertainties reflect the uncertainty in the integrated analysis substantially well. Although no SEs can be calculated for the

observed data, the Company has conducted a scenario applying a standard SE of 20% to all transition probabilities, for which the PSA remains similar to the updated base-case PSA, demonstrating the robustness of the transition probabilities.

B26. Can the company share what settings were changed to conduct the scenarios outlined in the company's response to CQ B24.

As highlighted in the company's response to Question B5, for the transition probabilities derived using the logistic model for month 12 to month 36, SEs were derived alongside the probabilities. For the transition probabilities before month 12, an average SE was calculated using the SEs from month 12-18 and is named TP_Var in the economic model ('Integrated analysis' Sheet, Cell AM31). As part of the company's response to Question B24, the impact of applying alternative SE values were explored.

To run the scenario where the company applied a SE of 20% to the transition probabilities from baseline to month 12 only, the value of the TP_Var was updated to 20%. Then, the PSA was rerun with the updated TP_Var value.

For the second scenario, where the company applied an SE of 20% to every transition probability, the TP_Var value remained at 20% for baseline to month 12 and for month 12 onwards formulas were added to calculate the SEs as 20% of the deterministic value. To run this scenario using the company's base-case settings, the formula for the SEs in cells AK74:AR153 and GJ74:GQ153 of the 'Integrated analysis' Sheet were directly updated to:

=Deterministic value*TP_Var

The PSA was then rerun with the updated TP_Var value. This has not been added as a switch in the company's economic model.

(B6 follow-up 04Dec24) Priority question. Please provide the proportion of patients with logMARs according to the economic model, who contributed to the mean logMARs reported in Table 11, 12 and 13 of the integrated statistical plan report using the Table format below. E.g. 20% of SoC patients in the

integrated analysis reported a logMAR between 1.3-1.7 at month 12 (this is an example and not a known proportion).

All patients who contributed to tables 11,12 and 13 of the integrated statistical plan report were included in the derivation of the transition probabilities for the economic model.

Please find below the proportion of patients in each health state at given timepoints as used in the results of Table 11, Table 12 and Table 13 of the Statistical Report, i.e the weighted not imputed population, the weighted MAR imputed population and the weighted MNAR imputed population, respectively.

The company would like to emphasise that the data included in Table 12 and Table 13 of the Statistical Analysis Report is generated data through imputation.

Transition probabilities used in the company's economic model from month 12 to month 36 were derived using multiple approaches. Transition probabilities for both treatment arms are based on weighted observations obtained from the integrated analysis, based on stabilised inverse probability of treatment weights, and derived using either:

- A logistic regression model (model dropdown: RHODOS/integrated data (logistic model, MAR)) or a weighted observed (model dropdown: RHODOS/integrated data (weighted observed, MAR)) approach using MAR MI which corresponds to the data in Table 12 of the Statistical Analysis Report (see Table 24 and Table 25 below), or;

- A logistic regression model (model dropdown: RHODOS/integrated data (logistic model, MNAR)) or a weighted observed (model dropdown: RHODOS/integrated data (weighted observed, MNAR)) approach using MNAR MI which corresponds to the data in Table 13 of the Statistical Analysis Report (see Table 26 and Table 27 below).

The company would like to note that when comparing the distributions of patients used for the analysis in Table 12 and Table 13 of the Statistical Analysis Report to the distribution of patients from the economic model, there may be some differences due to the transition probabilities derived from other sources being used before

month 12 i.e. RHODOS from baseline to month 6 and weighted observed transitions with no imputation from the integrated analysis from month 6 to month 12.

MMRM analysis, weighted, not imputed (Table 11 of the Statistical Analysis Report)

Table 22: Proportion of idebenone patients in each health state at each timepoint as derived from the MMRM analysis, weighted, not imputed (Table 11 of the Statistical Analysis Report)

Proportion of patients in each health state at given timepoints	Month 12	Month 18	Month 24	Month 36
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]
LP	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 23: Proportion of SoC patients in each health state at each timepoint as derived from the MMRM analysis, weighted, not imputed (Table 11 of the Statistical Analysis Report)

Proportion of patients in each health state at given timepoints	Month 12	Month 18	Month 24	Month 36
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]
LP	[redacted]	[redacted]	[redacted]	[redacted]

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

MMRM analysis, weighted, MAR imputed (Table 12 of the Statistical Analysis Report)

Table 24: Proportion of idebenone patients in each health state at each timepoint as derived from the MMRM analysis, weighted, MAR imputed (Table 12 of the Statistical Analysis Report)

Proportion of patients in each health state at given timepoints	Month 12	Month 18	Month 24	Month 36
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]
LP	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 25: Proportion of SoC patients in each health state at each timepoint as derived from the MMRM analysis, weighted, MAR imputed (Table 12 of the Statistical Analysis Report)

Proportion of patients in each health state at given timepoints	Month 12	Month 18	Month 24	Month 36
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]
LP	[redacted]	[redacted]	[redacted]	[redacted]

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

MMRM analysis, weighted, MNAR imputed (Table 13 of the Statistical Analysis Report)

Table 26: Proportion of idebenone patients in each health state at each timepoint as derived from the MMRM analysis, weighted, MNAR imputed (Table 13 of the Statistical Analysis Report)

Proportion of patients in each health state at given timepoints	Month 12	Month 18	Month 24	Month 36
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]
LP	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 27: Proportion of SoC patients in each health state at each timepoint as derived from the MMRM analysis, weighted, not imputed (Table 11 of the Statistical Analysis Report)

Proportion of patients in each health state at given timepoints	Month 12	Month 18	Month 24	Month 36
LogMAR <0.3	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.3-0.6	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 0.6-1.0	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.0-1.3	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR 1.3-1.7	[redacted]	[redacted]	[redacted]	[redacted]
CF	[redacted]	[redacted]	[redacted]	[redacted]
HM	[redacted]	[redacted]	[redacted]	[redacted]
LP	[redacted]	[redacted]	[redacted]	[redacted]

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

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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 16 May 2024. 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):	Joint response from patient experts James Ferguson, Lily Mumford and LHON Society

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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 16 May 2024. Please submit via NICE Docs.

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.	None
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Patient experts James Ferguson and Lily Mumford and [redacted] from LHON Society

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.
1	**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?**

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

Draft guidance comments form

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	The Equality Act 2010 covers England, Wales and Scotland and therefore it may be considered as potentially discriminatory against people living with LHON in England, given that residents of Wales and Scotland can access this drug. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** No, the model suggested by the EAG does not follow the characteristics of the condition. **Are the recommendations sound and a suitable basis for guidance to the NHS?** No **Section 1** We at the LHON Society feel that this recommendation lets down people living with a highly disabling condition. When surveyed (n=48), 98% of our members feel that there is strong unmet need for Idebenone to be available to people living in England, as it is in Scotland and Wales. 87% stated that this decision is inequitable. **Section 1.1** Idebenone is the only treatment option available and as such this decision will lead to further cases of people attempting to import unknown, potentially poor-quality versions of this drug from various sources at high costs. **Section 1.2** We strongly feel that this technology provides the only available treatment and this decision would affect the very few lucky people currently on treatment. **Section 3.1** The patient experts wish to reiterate their comments, LHON is a debilitating condition that leads to significant impacts on the persons life. **Section 3.2** There is a significant unmet need. 98% of survey respondents agree that there is an unment need for Idebenone in England **Section 3.3** People living with LHON try all sorts of Coenzyme Q10 supplements because NHS England do not provide Idebenone. In Scotland and Wales, this is not the case. People who can afford to often self fund these imported products thousands of pounds with he risk of considerable debt and hardship. **Section 3.10** The Patient experts and The LHON society wish to highlight the complete lack of understanding displayed by the EAG in their proposed modelling approach. This approach fails to recognise the disease, its characteristics and the ability of people classified as off-chart. We agree with the company and the committee request to

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

Draft guidance comments form

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	separate off-chart health utilities. The Patient experts also commented on the lack of understanding shown during the committee meeting by the EAG. **Section 3.15** We are confused as to why caregiver disutilities are not applied to adults in the model. When we surveyed our members 91% said that adults living with LHON need support and help to go about their daily lives. This clearly supports the need to account for caregiver disutility in the adult LHON population. A simple search of the literature demonstrates that a disutility for caregivers of adults would seem appropriate, ""Enoch et al (2022). What support do caregivers of people with visual impairment receive and require? An exploratory study of UK healthcare and charity professionals' perspectives"" gives a good account for this.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- 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.

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

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Single Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Name	[redacted]
Comments on the DG:	

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?

I just honestly feel the decision is a massive kick in the teeth for the people who have fought

Has all of the relevant evidence been taken into account?

No

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

Yes I was involved in the trials

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

No

General comment:
How much more evidence do you need that this medication DOES work?

How many other people do you want to suffer mentally whilst fighting for their sight?

Professor Patrick Yu Wai Man has worked tirelessly and others alongside to get this evidence.

I was on idebenone for 2 years and saw a dramatic change in my sight and have been off this for 4 months with stable vision.

I am completely and utterly disgusted on the decision. There are other companies in the world that are happy to fund this. I think this postcode

lottery as you like to call it is a fat joke. I for one will be going to back to my local mp who has helped get this to where it is and I will be going back to fight for this. You are wrong and have really lost my trust.

Name	[redacted]
Comments on the DG:	

"I note that a larger cohort is needed. However, from the evidence there is nothing to suggest that this medication does not work at all, meaning that there is a chance it can work for a select few.

1 in 50,000 people in the UK suffer from LHON. Moreover, its genetic meaning that over the years this number will increase.

I think you need to think about the return on investment compared to doing nothing. For example, this medication could save a % of patients' eye sight. Meaning that they wouldn't need help from the state. In comparison, doing nothing would mean that more people would need help from the state and NHS resources due to visual impairment and mental health issues as a snowball effect"

Name	[redacted]
Comments on the DG:	

1. It is near certain that Idebenone has some benefit to some patients but the lack of accurate or reliable data to calibrate this makes cost-effectiveness calculations imprecise at best. The most appropriate way to address this, therefore, is via the pricing mechanism.

2. The previous assessment by NHSE was improperly carried out as the economic factors which had supposed not to be assessed at that stage played a major (crucial?) role in its rejection by NHSE.

3. Consequently, patients have been failed, both by the company(ies) and by the NHSE assessment. Patients deserve better and are entitled to fair treatment.

4. Generic Idebenone is available on private prescription from UK pharmacies or at even less cost OTC from online health food suppliers in the USA or in Europe. Both of these pathways, however, require a degree of competence and financial standing on the part of patients in order to acess them, with the result that affluent and technically competent patients do have access to treatment, while those without these attributes have no such choice. Lack of approval for reimbursement therefore leads to inequality based both on income and access to computers. With imported OTC supplies there is a further risk of unregulated imported medication being of low

purity or possibly even contaminated. While I believe that risk is low (some patients have paid for periodic independent assays) it cannot be dismissed.

https://www.has-sante.fr/upload/docs/application/pdf/2022-06/raxone_190122_summary_ct19245.pdf

https://markets.ft.com/data/announce/detail?dockey=1330-1000781331en-07V6KLJLAE0D404UMEH2QRQQH9

https://supplements.relentlessimprovement.com/idebenone-p419.aspx

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

Draft guidance response

January 2025

Source of funding

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

1 Introduction

This document provides the External Assessment Group's (EAG's) critique of the company's response to the draft guidance (DG) for the appraisal of idebenone for treating visual impairment in Leber's hereditary optic neuropathy (LHON) in people aged 12 years and over (ID547).

Each of the issues raised in the draft guidance by the committee are outlined in Table 1, as are a summary of the company's response, and a summary of the EAG's critique of the company's response. Details of the company's response to the draft guidance are provided in Section 2 (clinical effectiveness) and 3 (cost effectiveness) of this report, as are the EAG's critique of the company's response to each issue.

The company's updated base case cost-effectiveness results and scenario analyses are provided in Section 4. The EAG's cost-effectiveness results and scenarios are provided in Section 5.

Finally, the EAG notes that following the DG, the company has updated the patient access scheme discount for idebenone to [redacted], updating the PAS price to [redacted] per pack.

Table 1. Issues for ACM2 and resolution status

Key issue		Status according to the EAG	Company approach	EAG
1	Comparator data and establishing relative treatment effects	Partially resolved	The company performed an integrated analysis by pooling all data sets across available LHON studies. The company conducted a PSWA to mitigate potential imbalances in prognostic factors between different data sources.	The EAG has several concerns with the company's methodology used to pool together the data sets into the integrated analysis, in addition to how the integrated data set has been analysed. Critically, the company has omitted the RHODOS RCT results from the integrated analysis and instead has applied the RHODOS and integrated analysis treatment effects separately in succession in the economic model, naively assuming that the two data sets are coherent. As such, the EAG considers that the treatment effect estimates may lack accuracy and validity.
2	Model structure	Unresolved	The company prefers to use the eight-state model as they consider the	The EAG considers that the four-state model should be preferred as it makes the

			integrated analysis to be sufficient to inform the high number of model transition probabilities.	most of the limited patient observations from RHODOS, which are used to inform treatment effects from baseline to six months instead of using of sequentially distinct data sources (RHODOs followed by the integrated analysis) in the company base case.
3	Treatment effects	Unresolved – key issue	Transition probabilities have been informed using RHODOS from baseline to six months and the integrated analysis from six to 36 months.	The integrated analysis should be used to inform treatment effects from baseline, with RHODOS included in the integrated analysis. The treatment effects observed in RHODOS and estimated from the integrated analysis are not accurately replicated in the model, with the model underestimating the SoC treatment effect.
5	Time on treatment	Unresolved – key issue	Derived from time to indication of treatment discontinuation from the integrated analysis.	Time to treatment discontinuation should be directly derived from time to treatment discontinuation and not time to *indication* of treatment discontinuation. The latter includes the company's clinical expert assumptions which the EAG considers inappropriate.
6	Patient HRQoL	Unresolved	The company considers that the health state utilities estimated from Lawrence *et al.* HUI-3 values are most appropriate to assume.[1]	The EAG considers that the Lawrence *et al.* EQ-5D health state utilities are more appropriate.[1]
7	Caregiver HRQoL	Unresolved	Included for all adults with logMAR>1 not in residential care till death.	Carer disutility should not be included.
8	Health state resource use	Unresolved	The frequency of health state resource use has been based on the difference between Meads *et al.* and the company's clinical expert opinions.[2]	Health state resource use should be based solely on Meads *et al.*[2] These frequencies reflect a much older population and are considerably less than the company's clinical experts assumed frequencies.

9	Probabilistic transition probabilities	Partially resolved	Transition probabilities can now be made probabilistic.	Transition probabilities can now be made probabilistic; however, treatment effectiveness uncertainty from RHODOS and the integrated analysis are not accurately reflected in the model.

Abbreviations: EAG, external assessment group; HRQoL, health-related quality of life; HUI, health utilities index, PSWA, propensity score weighted analysis.

2 Clinical effectiveness

2.1 Comparator data and establishing relative treatment effects

2.1.1 Integrated analysis of all available data

To address the lack of comparative data available between idebenone and standard of care (SoC), and the substantial limitations of the company's previously presented propensity score matching (PSM) analysis comparing the LEROS trial with data from CaRS-I and CaRS-II, the company performed an integrated analysis pooling all data sets across the available LHON studies (RHODOS, RHODOS-OFU, EAP, CaRS-I, CaRS-II, LEROS and PAROS).

The EAG notes such a comparison can be at high risk of bias due to imbalances in prognostic factors between patients from different data sources, such as differences in the prevalence of each LHON mutation type. To mitigate any imbalance in prognostic factors between idebenone and SoC groups, a propensity score weighted analysis (PSWA) was performed by the company, which the EAG notes can provide a less biased method to model the long-term treatment effect of idebenone compared to SoC.

2.1.2 Propensity score weighting analysis

2.1.2.1 Statistical methods (info from SAP)

The company's PSWA was weighted by stabilised inverse probability of treatment weights computed by a propensity score (PS) model. The following variables, at baseline, were incorporated into the propensity score models 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 the above baseline variables were excluded from analyses. The EAG notes that while its clinical experts had previously highlighted visual acuity at nadir as a potential prognostic factor of LHON, it has not been considered as a regression factor in the current analysis. In response to clarification questions, the company outlined that while they acknowledged that visual acuity at nadir was a potential prognostic factor, it was not possible to obtain data for this variable from the included registry studies.

Also, in response to a clarification question, the company noted that the PS models were used to align the baseline characteristics of the idebenone and SoC patient groups within the integrated analyses, as opposed to aligning the baseline characteristics of these patient groups to patients in the RHODOS trial (see Section 2.1.4 for further discussion). The adequacy of the PS models was assessed using assessment graphs (e.g., weight clouds, and visual comparisons of standardised mean differences) and results tables. When reviewing the assessment graphs, the EAG notes that there was broad alignment between the idebenone and SoC patient groups for weights and each of the prognostic variables. However, the EAG notes that the review of some assessment graphs (e.g., time from first onset at baseline; Figure 1) was challenging as the median and IQR were all in the range of 0 to ~25 months, while the figure axes extended to 600 months. Additionally, the EAG notes that after weighting, some differences in prognostic variables existed between the idebenone and SoC patient groups. For example, for the 12-month onwards analysis, the median time from first onset at baseline was 4.8 and 9.4 months in the weighted SoC and idebenone treatment arms, respectively. Accordingly, it is unclear how such a difference in a prognostic variable between the weighted patient groups will impact any analyses.

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 - Patients with at least one assessment at Analysis Visit 6 or 12 Month [+/- 3 Months])

The EAG notes that analyses of clinical efficacy were performed using patients within the ITT population who had at least one assessment on, or after, 12 months. Accordingly, this requirement resulted in all patients from the RHODOS trial being excluded from analyses of clinical efficacy. The EAG was concerned that all assessments from the RHODOS study were excluded from both analyses up to the 6-month visit and the 12-month visit onwards due to RHODOS being a randomised-controlled trial (RCT). In response to clarification questions, the company stated the RHODOS data have 'not' been excluded as they have been included in the economic model, with transition probabilities up to 6 months derived from RHODOS, but the EAG notes RHODOS data have not been included in the clinical integrated analysis. The EAG also notes that in response to clarification questions on clinical effectiveness, the company argues the integration of the RHODOS data with data from different study designs is not appropriate due to methodological differences between study types which could introduce bias. However, in response to clarification questions on cost-effectiveness, the company has made a conflicting argument, stating that RHODOS is the most appropriate data source for inclusion in the cost-effectiveness analysis, it being a RCT and providing the only head-to-head data directly comparing idebenone to SoC.

Considering that RHODOS was used to calculate transition probabilities for the first six months in the company's base case cost-effectiveness analysis, the EAG has concerns that RHODOS was not taken into account in the company's integrated analysis, in particular that the PSWA of the integrated data did not make the populations in the integrated analysis similar to those in RHODOS (i.e. naively assuming that the two datasets are coherent). This issue is discussed further in Section 2.1.4.

In addition, the EAG notes that although the company reports that PSWA for assessment up to 6 months was conducted, the results of this analysis were not presented to allow for a comparison between treatment effect estimates for up to 6 months from the integrated analysis and the results of the RHODOS trial (the duration of which was 6 months). Therefore, the EAG requested that the company provide the results of the 6-month analysis both including and excluding the RHODOS RCT to assess the above. However, the company did not provide these results and the EAG was unable to assess whether the 6-month results of the RHODOS trial aligned with the 6-month results of the integrated analysis or whether the economic model reflected the company's integrated analysis (see Sections 3.1 and 3.2 for further discussion).

Moreover, considering that the likelihood of spontaneous recovery is greater in patients with recent disease onset[3], the EAG has concerns that conducting separate analyses for up to 6-months and 12 months onwards and not presenting the former may obscure any potential benefit seen in SoC.

2.1.3 Modelling approaches

The company used imputation approaches to overcome the issue of missing data. For BCVA, three different approaches were performed using the weighted SET 2 population (where patients from the RHODOS trial had been excluded), consisting of all ITT patients with at least one assessment on or after the Month 12 analysis visit. Firstly, for change from baseline for BCVA, the company selected an mixed model for repeated measures (MMRM) without any explicit imputation as the base case model. In response to a clarification question, the company noted that MMRMs implicitly assume any missing data is Missing at Random (MAR). For change from baseline BCVA, two further sensitivity models, using multiple imputation (MI), were also performed. The first sensitivity analysis imputed missing data using a MAR approach, while the second sensitivity analysis imputed missing data using a Missing Not At Random (MNAR) approach. For both sensitivity analyses, once missing data was imputed, MMRMs were used to analyse the BCVA data. Across all MMRM models, treatment group, analysis visit, treatment-by-analysis-visit interaction, sex, LHON mitochondrial DNA (mtDNA) mutation, time from onset at baseline, laterality at baseline, and BCVA at baseline were included as fixed effects, while baseline BCVA-by-analysis-visit interaction was also included.

For clinically relevant benefit (CRB), analysis was performed using a logistic regression model using a logit link function. Analysis was performed using the weighted SET 2 population, as described above, where data had been imputed using the MAR and MNAR approaches. Separate models were fitted for the timepoints of 12, 18, 24, 30, 36, 42, and 48 months. Each model included treatment, sex,

LHON mtDNA mutation, time from onset at baseline, laterality at baseline, and BCVA at baseline as covariates.

In contrast to BCVA and CRB, clinically relevant recovery (CRR) was analysed using the SET 3 population, consisting of all ITT patients, excluding those enrolled in the RHODOS study, as the company indicated that no assumption of linearity was required for this endpoint. Accordingly, time to CRR was presented in the form of a Kaplan-Meier (KM) chart with the KM product-limit method used to showcase event probabilities in the treatment groups. Likewise, time to indication for treatment discontinuation was analysed using patients in the SET 3 population (where patients from the RHODOS trial had been excluded) who received idebenone. As with time to CRR, time to indication for treatment discontinuation was presented in the form of a KM chart with the KM product-limit method used to showcase event probabilities in this patient group.

The EAG is concerned that, for the imputation in the integrated analysis performed for the outcome of change in BCVA from 12-months onwards, the company opted for an approach with an implicit MAR assumption citing the rarity of LHON and the nature of the natural history (LEROS) study, but with no tests carried out to determine if data were MAR. The EAG notes that MAR is a strong assumption to make and considers the company's justification for using an MAR approach over a MNAR approach insufficient. The EAG also notes that when explicit MAR and MNAR approaches were used (results available in the Integrated Statistical Analysis [ISA] Report), the magnitude of the treatment effect of idebenone was substantially reduced while uncertainty (standard error) increased, compared to results for the base case MMRM approach that has an implicit assumption of MAR. Thus, considering the company's lack of robust justification for selecting an implicit MAR approach and the more favourable results of this approach compared to the explicit MAR and MNAR approaches, the EAG is concerned that the company's choice of base case model could be at risk of bias and that it may have been results driven.

At clarification, the EAG requested that the company present relevant test results to support the MAR assumption. In response to the EAG's clarification questions, the company did not carry out tests to support the MAR assumption suggesting there is no consensus on the tests that can be performed to check this assumption. Moreover, in response to clarification questions, the company noted that differences in the estimates between assumptions were expected as a result of different plausible values estimated for the missing values and that any differences observed were not biased in favour of any treatment group. The EAG agrees with the company's observation that the

estimated difference of idebenone vs SoC (and the corresponding SE) was similar across models (regardless of whether imputation was performed) but notes that results for individual arms were more favourable for idebenone in the company's chosen model. Thus, with more favourable data for idebenone from the company's chosen implicit MAR approach and with no robust justification for the choice of this approach, the EAG considers that the MNAR approach to be the least biased.

The EAG notes that multiple imputation was only performed from 12 months onwards. A total of 302 idebenone patients and 240 SoC patients were included in the analyses of change in BCVA in logMAR and CRB (i.e. SET 2, consisting of all ITT patients with at least one assessment on or after the Month 12 analysis visit). In response to clarification questions, the company provided the number of patients meeting this criterion at each time point. These are presented in Table 2 below.

Table 2. Number of patients with at least one assessment at each timepoint by treatment group in the analysis set used for the change in BCVA in logMAR and CRB (reproduced from Table 1 in the company's clarification response)

Frequency	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48+
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA, best corrected visual acuity; CRB, clinically relevant benefit; logMAR, logarithm of the minimum angle of resolution; SoC, standard of care.

The EAG notes that the number of patients with available data declines over time with a substantial decrease noted in the number of patients with data available after month 24. Accordingly, the number of patients for whom data was imputed becomes increasingly larger over time. In addition, in the company's response to clarification questions, the EAG notes the very small number of patients ([redacted] in total across treatment groups) with complete data in all variables of interest across all timepoints. The EAG acknowledge that LHON being a rare disease can impact the availability of patient data but considering that the drop-out rate appears to be substantially higher after month 24, with the proportion of patients with data available at month 30 being less than 20% in the idebenone arms and less than 15% in the SoC arm, and decreasing further at month 36 and month 42, the EAG is concerned that the large loss of data and hence the large amount of imputed data over time may impact the robustness of the treatment effect estimates.

For the clinical endpoint of BCVA, the company stated that all assessments up to the 6-month analysis visit were analysed separately from the assessments performed at 12 months onwards. The company justified this decision by noting that studies of the natural history of LHON indicate that

patients typically experience a rapid deterioration in disease progression until nadir which is then followed by a stabilisation period followed by some cases of spontaneous improvement. Accordingly, the company outlined that it was not appropriate to implement assumptions of linearity when modelling change in BCVA and elected to compensate for this by removing all data measured at assessments before 12 months. The EAG notes that analyses of BCVA were performed using linear mixed models with repeated measures (MMRMs). However, as opposed to excluding 6-month data, the company may have instead accounted for any non-linearity within the integrated analyses by implementing non-linear MMRMs.[4]

2.1.4 Baseline characteristics

The baseline characteristics of the matched patients (weighted by PS weights) from the weighted analysis (SET 2), used for the MMRM and MI modelling are displayed in the table below. The EAG notes that idebenone patients from the RHODOS-OFU study were excluded and only assessments for the SoC from RHODOS-OFU have been included. The EAG considers this was appropriate considering the observational nature of RHODOS-OFU, where patients were no longer on treatment but also notes that there was a small number of patients who reported the use of idebenone during the RHODOS-OFU follow-up. However, the number of patients, who reported using idebenone, in the SoC arm was very small (n=2) and it is unclear whether these patients were included in the present integrated analysis. Thus, the EAG has no concerns that this may have impacted the treatment effect of idebenone compared to SoC. A total of 302 idebenone patients and 240 SoC patients were included.

As discussed earlier, in response to clarification questions, the company confirmed that matching was performed solely to align the baseline characteristics between the treatment groups and not to align the baseline characteristics of patients in the integrated analysis with those from RHODOS. However, the EAG notes that transition probabilities for the first six months in the company's cost-effectiveness analysis were based on RHODOS. As such, the EAG is concerned that RHODOS was not taken into account in the MMRM and notes the PSWA could have been based on the RHODOS RCT baseline characteristics. Accordingly, this would ensure that baseline characteristics are aligned across all analyses, rather than the trials underpinning the integrated analysis. The baseline characteristics of the ITT population of the RHODOS RCT are also provided in the table below, for comparison purposes.

Table 3. Baseline characteristics from the weighted analysis (adapted from Table 1 in the company's DG 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		[redacted]	[redacted]	NR	NR
Time from first on set at baseline (months), mean		[redacted]	[redacted]	22.8	23.7
Baseline best visual improvement (logMAR), mean		[redacted]	[redacted]	1.61	1.57

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

The EAG considers the baseline characteristics of matched patients, including age at first symptom onset and the prevalence of the milder T14484C genotype which remained unbalanced in the company's previous PSM analysis, to be reasonably balanced between treatment arms. The EAG notes the proportion of male patients did comprise the vast majority but was relatively lower compared to patients in the RHODOS trial, which the EAG's clinical experts considered to most 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 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) with the prevalence of mutations being almost equal to one another in the current analysis whereas in the RHODOS trial it was higher for the m.14484T>C (compared to m.3460G>A), which is associated with the greatest probability of spontaneous visual recovery. [3] In addition, a number of patients with other mutations, not present in the RHODOS trial

([redacted] patients in the weighted population), were included in the current analysis. 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 mean time (months) from first onset was higher compared to the RHODOS trial. The EAG notes that the standard deviation (SD) and range for time (months) from first onset, available in the company's ISA report ([redacted] to [redacted] for idebenone vs [redacted] to [redacted] SoC) were not aligned with the range and SD reported for months since onset of vision loss for the RHODOS ITT, which appeared to be much smaller. In addition, the range in length of time since first onset being very wide in the current weighted analysis may suggest the sample included patients across the subacute, acute, dynamic and chronic phases of LHON. However, the mean time from first onset being >1 year and the mean baseline best logMar being ≥1.0 suggests the majority in the population of matched patients was most likely representative of prevalent LHON patients at the chronic phase of the disease and less likely of the earlier subacute/acute and dynamic phases.

In addition, the EAG notes that the company had not presented variance data (SDs or range) for the data provided for each parameter in their response. In response to clarification questions, the company pointed the EAG towards where these were provided in the company's ISA report. The EAG is concerned that, although the proportion of patients and mean estimates for each parameter in the current analysis were matched between the idebenone and SoC arms, the SDs differed considerably between arms for time from first onset at baseline ([redacted]) indicating substantial within group variation for this variable (see Section 2.1.5 for further discussion).

Lastly, the EAG identified a small discrepancy in the values reported for time from first onset at baseline for the idebenone arm, between the table of baseline characteristics the company provided in their response (Table 3 above) and the more detailed table of baseline characteristics of SET 2 included in the ISA report. The EAG asked a clarification question regarding this disparity to the company, however an explanation for the discrepancy was not provided.

2.1.5 Disease stage at baseline

The natural history of LHON has been clearly defined by previous studies.[5] Following the onset of the disease, patients experience a rapid deterioration in visual acuity up to a nadir that may occur between 4 to 6 months after the onset of symptoms.[6] Following the nadir, patients may experience a slow stabilisation of visual acuity. However, in some cases, patients may experience an increase in

visual acuity associated with a spontaneous recovery event. As shown by Table 4. below, the company has defined a patient's baseline BCVA relative to the start of treatment with idebenone, SoC, or a placebo. Accordingly, the EAG notes that a patient's baseline visual acuity may have been measured at any stage of the disease's natural history (e.g., pre-rapid deterioration, during rapid deterioration, at nadir, during stabilisation). As such, the EAG is concerned that while the company has accounted for time since onset at baseline, disease stage has not been adequately accounted for.

Within the ISA report, the company has provided mean, median, and range for time from first onset at baseline for the weighted analysis populations (shown in Table 4. below). Accordingly, for the idebenone and SoC groups, the median time since onset was [redacted] and [redacted] months respectively. Likewise, for the idebenone and SoC groups, the interquartile range for time from first onset at baseline was [redacted] to [redacted] months and [redacted] to [redacted] months, respectively. Consequently, it is anticipated that each of the treatment groups comprises patients where baseline corresponds to different disease stages. Given the above, the EAG is concerned that treatment effects may not be consistent across patients entering studies at different stages of the disease and the appropriateness of combining such patients into a single cohort. As such, the EAG is concerned that disease stage at baseline may be a treatment effect modifier for change from baseline BCVA that is unaccounted for within this analysis.

However, the EAG notes that there is no evidence (e.g., subgroup analyses of patients with differing baseline time since first onset) to illustrate inconsistent, or consistent, treatment effects across disease stages. In response to a clarification question, the company noted that disease stage was accounted for in both the propensity score weights and in the regression models through the prognostic variables of visual acuity at baseline and time since onset at baseline. As such, the company noted that they have assumed that baseline differences in disease stage have been accounted for through these variables.

Table 4. Descriptive weighted statistics of Time from First Onset at Baseline for the Integrated analysis ITT patients with at least one assessment in Analysis Visit 12 Month (adapted from the company's ISA Report table: Descriptive WEIGHTED statistics on patients with at least one assessment in Analysis Visit 12 Month [+/- 3 Months] or after)

	Idebenone (N = 302)	SoC (N = 239)
Mean Time from First Onset at Baseline (Months) [Standard Deviation]	[redacted]	[redacted]

Median Time from First Onset at Baseline (Months)	[redacted]	[redacted]
Range of Time from First Onset at Baseline (Months)	[redacted]	[redacted]
Interquartile Range of Time from First Onset at Baseline (Months)	[redacted]	[redacted]

Abbreviations: ITT, Intention-to-Treat; SoC, standard of care.

The EAG considers that while time since onset may potentially be a proxy for disease stage, other prognostic variables (e.g., time since nadir) are likely to better indicate a patient's disease stage although they were not considered by the company. In response to a clarification question, the company acknowledged the importance of considering a patient's nadir. However, the company noted that this was not possible to consider a patients' nadir in the presented analyses due to an inability to determine when nadir occurred in the included registry studies.

2.1.6 Off-chart logMAR value selection

The EAG notes that there are multiple different scales regarding how off-chart logMAR values are defined and that the company had not clarified how the scale had been selected.[7] In response to a clarification question, the company agreed that there are multiple different scales which may have been chosen, although there is no consensus on the best scale within the field. The company outlined that the chosen off-chart logMAR values represented the mid-point of the ranges used within the health scales included within the cost-effectiveness model. However, the EAG notes that uncertainty remains as to how the logMAR values for the cost-effectiveness model were selected in the first instance.

The EAG notes that for the off chart logMAR classes, there were consistent differences of 0.3 logMAR between 'finger count', 'hand motion', and 'light perception'. However, the difference between 'light perception' and 'no light perception' equates to a difference of 0.55. In response to a clarification question, the company responded that 'no light perception' is frequently assigned a value of 3.0 logMAR which was applied in this analysis too; although the EAG notes that no reference was provided for this statement. However, the EAG notes that by not selecting an equivalent 'mid-point', the change from 'no light perception' to 'light perception' would numerically be viewed as an improvement approximately twice that of transitioning from 'light perception' to 'hand motion'. The EAG is unsure whether such a numerical change is clinically valid. In response to a clarification question, the company noted that only two patients were imputed as having a logMAR of 3.0 and that this health-state was not included in the economic model.

2.1.7 Outcomes from the integrated analysis

2.1.7.1 Change from baseline in BCVA

For the analysis of change in BCVA in logMAR, three different modelling approaches were performed, discussed in Section 2.1.3. These were performed using the weighted SET 2 population (where patients from the RHODOS trial had been excluded), consisting of all ITT patients with at least one assessment on or after the Month 12 analysis visit.

A MMRM without multiple imputation was chosen as the company's preferred analysis, which as highlighted by the company in response to clarification questions, implicitly assumes any missing data are MAR. Treatment group, analysis visit, treatment-by-analysis-visit interaction, sex, LHON mtDNA mutation, time from onset at baseline, laterality at baseline and BCVA at baseline were included as fixed effects, while baseline BCVA-by-analysis-visit interaction was also included.

The MMRM analysis produced estimates for 6-month intervals from month 12 to month 48. The EAG notes that for each 6-month study time point, study visits may have occurred within three months before or after the given time point. For instance, the 6-month time point may comprise study visits between 3 months and 9 months from baseline. However, no data are available in the ISA report regarding the number of observations for each timepoint that were at the lower, middle, and upper ends of the stated visit window. As such, it is unclear to the EAG whether the effect of idebenone, or SoC, would be sufficiently consistent across a 6-month period to allow data to be combined into a single timepoint.

The estimated change from baseline in BCVA in logMAR and the estimated difference in BCVA in LogMAR for idebenone and SoC from baseline is presented in Table 5 below. A visual analysis of Table 5 is provided below, in Figure 2.

Table 5. Change in BCVA in logMAR derived from the integrated analysis as measured by the base case MMRM analysis (reproduced from Table 2 in the company's DG response)

Analysis visit	Estimated change in logMAR ± SE (95% CI)		Estimated difference in logMAR ± SE (95% CI)	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: CI, Confidence interval; logMAR, Logarithm of the minimum angle of resolution; MMRM, Mixed models for repeated measure; SE, Standard error; SoC, Standard of care

Figure 2. Change in BCVA in logMAR derived from the integrated analysis as measured by the base case MMRM analysis (reproduced from Figure 1 in the company's DG response)

Abbreviations: BCVA, Best corrected visual acuity; logMAR, Logarithm of the minimum angle of resolution; MMRM, Mixed models for repeated measures; SoC, Standard of care

The EAG notes that as demonstrated by the results of the base case MMRM model in Table 5 and Figure 2, at month 12, there was a slight improvement in logMAR in the idebenone group of [redacted] (95% CI: [redacted]) while in the SoC group there was a worsening of logMAR of [redacted] (95% CI: [redacted]

[redacted]). The between-group difference of [redacted] (95% CI: [redacted]), which translated to an improvement of [redacted] letters on the ETDRS chart and was statistically significant in favour of idebenone (p<[redacted]).

Similar results were observed in subsequent time points at month 18 and month 24 as the between-group difference remained statistically significant in favour of idebenone, despite the worsening noted in the SoC group decreasing compared to that noted at 12 months. At month 30, no further improvement in logMAR compared to the previous time point was observed in the idebenone group but the between-group difference of [redacted] was statistically significant [redacted] Based on Table 2 presented earlier, the EAG notes the substantially reduced number of patients with data available from this time point onwards compared to previous time points, which also differed between treatment groups (approximately 20% vs 15%, for idebenone and SoC, respectively) and hence the large proportion of missing data that may be affecting the robustness of the treatment effect estimate.

At month 36, the treatment effect of idebenone was reduced compared to previous time points. The estimated mean change in SoC patients also decreased which the company noted was due to the spontaneous recovery observed in some patients. The between-group difference of logMAR [redacted] did not reach statistical significance (p=[redacted]) but the company noted results were still in favour of idebenone.

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

2.1.7.2 Achievement of clinically relevant benefit (CRB) and time to first clinically relevant recovery (CRR)

The EAG notes that to demonstrate the effectiveness of idebenone, the company defined a CRB to include meeting criteria for a CRR, defined as achieving a pre-specified amount of improvement in BCVA from baseline, or a clinically relevant stabilisation (CRS) of visual acuity, defined as maintaining a baseline BCVA that is less than 1.0 logMAR (i.e., retaining the status of not being legally blind).

Thus, CRB was defined as any of the following, where the first two scenarios involve CRR and the third involves CRS:

- An improvement of at least 2 lines (10 letters) in BCVA; that is, if:
    - baseline BCVA < 1.7 logMAR and post-baseline Visit BCVA Change versus baseline ≤ –0.2 logMAR.
- A change from off-chart to on-chart results by at least 5 letters; that is, if:
    - baseline BCVA ≥ 1.7 logMAR and post-baseline Visit BCVA ≤ 1.6 logMAR.
- For those patients with a baseline BCVA < 1.0 logMAR, the maintenance of that BCVA: that is, if:
    - baseline BCVA < 1.0 logMAR and post-baseline Visit BCVA < 1.0 logMAR.

As described earlier, analysis of CRB was performed using the weighted SET 2 population where data had been imputed using the MAR and MNAR approaches. Separate models were fitted for the timepoints of 12, 18, 24, 30, 36, 42, and 48 months. Each model included treatment, sex, mutation, time from onset at baseline, laterality at baseline, and BCVA at baseline as covariates. CRB was analysed using a logistic regression model, weighted by stabilised inverse probability of treatment weights. The odds ratio of CRB with idebenone versus SoC at each time point from month 12 onwards, using results from the MI MAR analysis, is presented in Table 6 below.

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 (reproduced from Table 3 in the company's DG response)

Analysis visit	Idebenone vs SoC		
	Odds ratio	Odds 95% CI	Odds ratio p-value
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

The EAG notes that at month 12, patients on idebenone were almost 3 times more likely to have a CRB compared to SoC patients, a result which was statistically significant but the magnitude of which was not maintained in subsequent time points. The EAG notes that there was alignment in the odds

ratios (and associated confidence intervals) reported by both the MI MAR and MI MNAR analyses. In addition, the EAG notes the great decline in the number of patients with available data over time displayed in Table 2 which may have influenced the robustness of effect estimates.

Time to first CRR (in months) was the variable of interest in the company's integrated analysis. This was defined as follows: (date of first CRR – date of baseline assessment +1) / 30.4375. In contrast to BCVA and CRB, CRR was analysed using the SET 3 population, as the company indicated that no assumption of linearity was required for this endpoint. Accordingly, time to CRR was presented in the form of a KM chart with the KM product-limit method used to showcase event probabilities in the treatment groups. The time to first CRR for each treatment group based on KM analysis is presented below.

Table 7. Time to first recovery in BCVA (reproduced from Table 4 in the company's DG response)

	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48
Idebenone							
At risk, weighted n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KM (SE), %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC							
At risk, weighted n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KM (SE), %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan-Meier; SE, Standard error; SoC, Standard of care

The probability of attaining CRR over time from baseline is displayed in Figure 3 below.

Figure 3. Time to first recovery in BCVA using KM analysis and weighted log rank test (reproduced from Figure 2 in the company's DG response)

The company notes that the estimation of patients who met the definition of CRR responder increased with time for both treatment groups, with the proportion of patients being consistently higher in the idebenone group compared to SoC, thus further supporting the efficacy of idebenone. In addition, the idebenone group appeared to each CRR significantly faster than the SoC group (p=). However, as previously highlighted in the EAG report, the EAG has concerns about CRR and the extent to which it constitutes a good indication of the effect of treatment with idebenone. That is because a considerable proportion of patients in the SoC arm met the definition of CRR without receiving treatment, which may suggest CRR could have also been a result of spontaneous recovery.

In addition, considering the definitions of CRB and CRR described above and that they are based on patients' baseline BCVA, CRB and/or CRR may be achieved with no difference in functional sight or change in HRQoL (patients are still considered vision impaired or unable to conduct key autonomous functions such as driving). Therefore, CRR may not be a helpful indicator of improved HRQoL as it does not differentiate between sight recovery and functional sight recovery. To examine this further, the EAG requested that the company provide the number of patients who fall under each logMAR category based on their baseline BCVA and the number of patients in each category that were deemed to have a CRB or CRR. The company was unable to provide these data, highlighting that as analyses were run based on PS weights, the resulting observations constituted patients' weights and not actual patients. In addition, CRB and CRR analyses were performed based on MI datasets and as

a result, the number of patients with the outcomes at each visit may not necessarily correspond to the number of observed patients and could include imputed results.

2.1.7.3 Time-to treatment-discontinuation

The EAG notes that time to indication for treatment discontinuation from the company's integrated analysis was used to inform time on treatment within the company's cost effectiveness base case model (See Section 3.3). This was defined as the time from first dose to when the treatment should be stopped according to clinical expert opinion and was analysed using patients in the SET 3 population who received idebenone. As with time to CRR, time to indication for treatment discontinuation was presented in the form of a KM chart with the KM product-limit method used to showcase event probabilities in this patient group.

Results of the KM analysis for the time to indication for treatment discontinuation are presented in Table 8 and

Figure 4 below. Time to indication for treatment discontinuation was used to inform time on treatment calculation in the company's base case.

Table 8. Time to indication for treatment discontinuation product-limit estimates (ITT population, SET 3, idebenone patients)

	12 Month	18 Months	24 Months	30 Months	36 Months
At risk, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KM (SE), %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM, Kaplan-Meier; SE, Standard error.

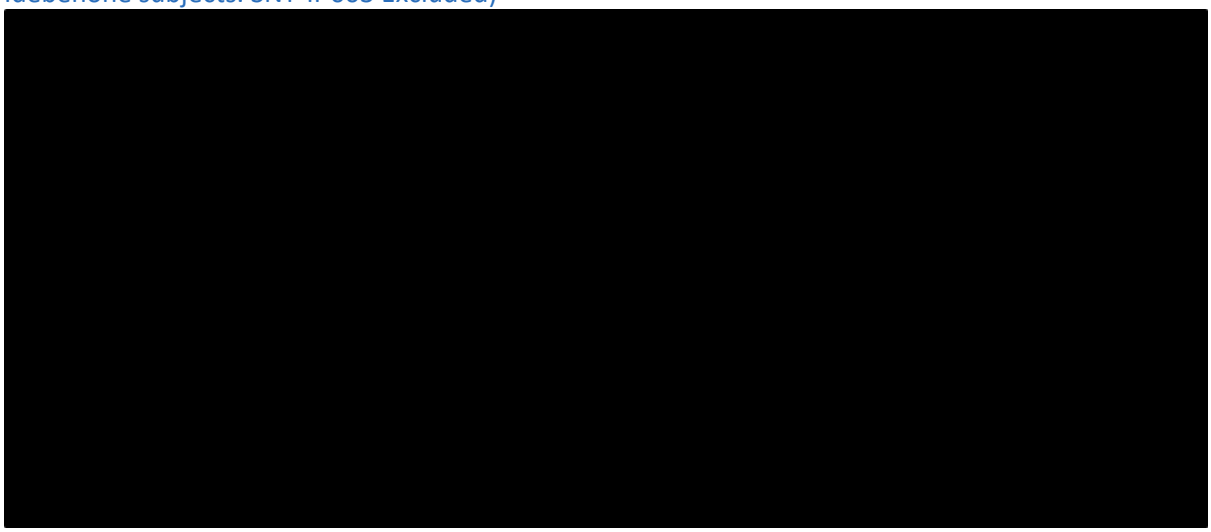
Figure 4. Time to indication of treatment discontinuation (reproduced from the company's ISA Report: Time to Indication for Treatment Discontinuation - Kaplan Meier Analysis Integrated ITT. Idebenone subjects. SNT-II-003 Excluded)

Based on

Figure 4, the EAG notes that the median time to indication for discontinuation was approximately 24 months. Additionally, at 12 months all patients (%) were not indicated for treatment discontinuation, while at month 27 over % of patients were indicated for treatment discontinuation. However, as discussed further in Section 3.3.1, the EAG considers time to treatment discontinuation (presented in Figure 5 below), defined as the time from first dose to treatment discontinuation, to be more reflective of patient time on treatment compared to time to indication for treatment discontinuation as it shows when patients actually discontinued treatment and not when patients should have discontinued treatment according to the company's clinical experts.

Figure 5. Time to treatment discontinuation – Kaplan Meier Analysis (reproduced from the company's ISA Report: Time to Treatment Discontinuation – Kaplan Meier Analysis Integrated ITT.

Idebenone subjects. SNT-II-003 Excluded)



2.1.8 Conclusions of the clinical effectiveness evidence

Despite the company performing an integrated analysis pooling all data sets across the available LHON studies (RHODOS, RHODOS-OFU, EAP, CaRS-I, CaRS-II, LEROS and PAROS) and a PSWA to mitigate imbalances in prognostic factors between data sources, the EAG still has concerns about the robustness of the treatment effect estimates.

The EAG is concerned that the PSWA was used to align the baseline characteristics of the idebenone and SoC patient groups within the integrated analyses with no consideration for matching to RHODOS. The company did not include RHODOS in the integrated analysis as they considered the RCT-design makes it inappropriate for inclusion. However, the company considered it appropriate to use RHODOS for the analysis of the first 6-months in the economic model followed by the results of the integrated analysis with no adjustment (i.e. naively assuming that the two datasets are coherent). The EAG notes that although the company reports that PSWA for assessment up to 6 months was conducted, the results of this analysis were neither presented in the company's DG response nor provided by the company in response to clarification questions. As such the EAG was unable to explore the impact of this dissimilarity between the two datasets used in the economic model. The EAG considers that due to the differences in the baseline characteristics between the two datasets, it unlikely that the current approach is coherent. Likewise, the EAG was unable to assess whether the 6-month results of the RHODOS trial aligned with the 6-month results of the integrated analysis or to compare the integrated analysis results with the results of the economic analysis where RHODOS data has been used to calculate transition probabilities.

Moreover, considering that the likelihood of spontaneous recovery is greater in patients with recent disease onset, the EAG has concerns that conducting separate analyses for up to 6-months and 12 months onwards and not presenting the former analyses, may obscure the potential benefit seen in SoC.[3] The EAG's preferred approach would be to match participants of the integrated analysis with those of the RHODOS RCT (and so ensure that a coherent population is used as the basis for the transition probabilities in the economic model). In the absence of this preferred approach, the EAG would have wanted to see the results of 6-month integrated analysis to compare them with those of the RHODOS RCT (the duration of which was 6-months) to be able to assess the consistency of the results and use that as a surrogate to determine the robustness of using of sequentially distinct data sources (RHODOs followed by the integrated analysis) in the economic model.

In addition, the EAG is concerned that the large loss of data noted overtime 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 notes this as a limitation potentially impacting the robustness of the treatment effect estimates. Within this framework, the EAG considers the company's justification for using a MAR approach over a MNAR approach insufficient and MNAR approach to be the least biased. The EAG notes that although the absolute treatment effects across models were consistent, when looking at the relative treatment effect for each arm, the benefit seen for idebenone in the EAG's preferred approach, was less favourable compared to the company's preferred MAR approach. Thus, the EAG still has concerns that the choice of modelling approach may be inappropriate; however, the EAG notes that the overall impact, of selecting a MAR approach over an MNAR approach, on the treatment effect estimates may be small.

Lastly, considering that the company defined patients' baseline BCVA relative to the start of treatment, which signifies that baseline visual acuity may have been measured at any stage of the disease, the EAG is concerned that while the company has accounted for time since onset at baseline, disease stage has not been adequately accounted for. Noting variability in the median and interquartile range of time since onset between idebenone and SoC groups, the EAG is concerned that in each treatment group, baseline corresponds to different disease stages. Consequently, disease stage at baseline is a potential treatment effect modifier that has not been adequately accounted for in the company's integrated analysis. Although in response to clarification questions, the company noted disease stage was accounted for through the prognostic variables of visual acuity

and time since onset at baseline, the EAG considers that other prognostic variables such as time since nadir are likely to be better indicators of disease stage. The EAG acknowledges that due to limitations in the current data, it was not possible to consider a patient's nadir in the presented analyses due to an inability to determine when the nadir occurred in the included registry studies; however, the EAG still has concerns that disease stage at baseline may be a treatment effect modifier not fully accounted for in the analyses.

3 Cost effectiveness

3.1 Model structure

In the company's previous base case, an eight-health state Markov model was assumed as it was thought to best capture the deterioration of vision in terms of logMAR. The EAG considered that there were insufficient data from the RHODOS trial and the EAP study to inform the high number of transitions in the eight-state model, which led to some health state transitions being impossible (0% probability) and others guaranteed (100% probability). The EAG therefore preferred a four-state model which was considered to make the best use of the limited available data.

The committee stated in the DG that they agreed with the EAG that, "*the high number of health states but limited observed transitions increases the uncertainty of a model structure*" but also noted that, "*transitions between counting fingers and states with higher VA would be associated with a significant benefit that would not be captured in a less sensitive model*". The committee therefore requested further analyses that showed the sensitivity of the model to transitions, particularly for lower visual acuity (VA), and to explore the robustness of transition probabilities in both model structures.

In the company's response to the DG, the company remains of the opinion that their proposed eight-state model is robust clinically and economically and is suitable for decision-making. They note that their model has already been subject to comprehensive assessment from other global HTA bodies such as the Scottish Medicines Consortium (SMC), All Wales Medicines Strategy Group (AWMSG) and National Centre for Pharmacoeconomics (NCPE) and has been accepted each time.

The company additionally considers that the four health state model lacks distinction between VA levels and presents an unreasonably simplified interpretation of such a complex and debilitating disease. While the EAG preferred model does reflect HST 11,[8] the company suggested there are substantial differences between this appraisal and HST11, such as the patients being modelled.

Given that the committee's modelling concerns were due to the lack of available data to inform the transition probabilities of the eight-state model. The company in their updated base case derived transition probabilities using the integrated analysis which combines the relevant idebenone studies into a singular integrated data set. Table 9 presents the number of patient observations from the

integrated analysis for each treatment per time point. The company were therefore confident that the size of the integrated analysis supported the use of the eight-state model.

Table 9. Integrated analysis patient observations

	Patient observations		
Visit (month)	Idebenone	SoC	Total
6	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]
48+	[redacted]	[redacted]	[redacted]

Abbreviations: SoC, standard of care.

To address the committee's request for further analyses that show the sensitivity of the model to the number of transitions, the company conducted a scenario using the four-state model. Compared to the eight-state model, the four-state model led to an increase in the ICER of approximately £4,000, increasing the ICER above the £30,000 cost effectiveness threshold.

3.1.1 EAG critique

The EAG agrees with the company that the larger number of patient observations in the integrated analysis helps to mitigate the issues caused by the small number of observations informing the large number of transition probabilities. However, the EAG is still concerned that there are too few observations even with the integrated analysis to inform the eight-health state model. As presented in Table 9, by month 30 there are [redacted] observations to inform [redacted] transitions (from eight health states to eight health states for both idebenone and SoC patients).

More critically however is that while Table 9 highlights that [redacted] ([redacted] idebenone and [redacted] SoC) observations are available to inform transitions from baseline to six months, the company in their updated base case has informed these transitions using RHODOS. Comparatively, [redacted] idebenone and [redacted] SoC patient observations (including required imputations due to missing data) are available from RHODOS compared to the [redacted] and [redacted] available from the integrated analysis, respectively.

As such, while the company states that the integrated analysis supports the use of the eight-state model, the EAG considers that as the integrated analysis has not been used to inform the model

from baseline, but instead the considerably smaller data set from RHODOS, the eight-state model does not make best use of the available data and is therefore inappropriate.

As a consequence of this, and as was true in the company's previous base case, when informing the model using RHODOS from baseline to six months, due to the small numbers of patient observations (as little as a single observations in multiple instances), transitions between health states can be certain and impossible, resulting in health state occupancies of zero within the first year of the model (Table 10). The EAG considers this to be clinically implausible.

Table 10. SoC health state occupancy using RHODOS and the eight-state model

Years	Cycle	Population								
		LogMAR <0.3	LogMAR 0.3-0.6	LogMAR 0.6-1.0	LogMAR 1.0-1.3	LogMAR 1.3-1.7	CF	HM	LP	Dead
0	0	[redacted]								
0	1	[redacted]								
0	2	[redacted]								
0	3	[redacted]								
1	4	[redacted]								

Abbreviations: CF, counting fingers; HM, hand movement; LP, light perception.

The EAG similarly notes there is considerable uncertainty associated with the health state utilities and costs, leading to substantial overlapping and production of clinically implausible differences between health states in the PSA iterations. The EAG therefore considers that a reduced model may be more appropriate as it allows for substantially fewer transitions, while retaining the key clinically important changes, leading to lower data requirements but higher precision of outcomes.

In the DG, the committee, "*asked for analyses that explore the robustness of transition probabilities in both model structures. In particular, separating off-chart health states in the EAG model structure, especially for counting fingers VA, would be helpful*". Therefore, at clarification the EAG requested the company to conduct a scenario using the which separated the previously grouped off-chart health states (counting fingers, hand movement, light perception) in the four state model. In their response, the company reiterated that the eight-health state model structure is clinically and economically plausible for decision-making in patients with LHON and that it was highly inappropriate to merge logMAR health states together. As such, no scenario using the requested model structure was conducted.

The EAG considers that a model structure separating the off-chart health states while combining health states with similar quality of life (QoL) and cost values would have been most appropriate and would have aligned with the committee's preferences from ACM1; however, as a scenario was not provided or the functionality added to the model for the EAG to conduct the scenario, only the eight or four health state model can be assumed. Given the use of RHODOS to inform treatment effects from baseline to six months, resulting in the health state occupancies in Table 3 which the EAG considers clinically improbable, coupled with the quality of life (QoL) and cost overlap between similar logMAR health states; the EAG considers the four-health state model is more appropriate for decision making and is used to inform the EAG base case.

3.2 Treatment effects

In the company's previous base case, idebenone treatment effects were derived using RHODOS from baseline to six months. From month six to 36 months, treatment effects were informed using the EAP real-world evidence study. The EAG had concerns with the use of RHODOS and the EAP study to inform treatment effects given the availability of the LEROS study, which represented a larger patient population (199 patients in LEROS compared to 87 in RHODOS and EAP). In the EAG base case, idebenone treatment effects were informed using LEROS.

SoC treatment effects in the company's previous base case were also derived using RHODOS from baseline to six months, with natural history CaRS-1 patients used to supplement RHODOS up to 36 months. The EAG originally preferred to derive a SoC treatment effects using a combination of CaRS-I and CaRS-II patients; however, when comparing the outcomes of the economic model to those reported in RHODOS and CaRS studies, the model was found to greatly overestimate the deterioration of logMAR and underestimate logMAR recovery for SoC patients, leading to an underestimation of the ICER. This was due to the company's imputation of the data, which used a last observation carried forward assumption, leading to over 60% of the SoC observations being imputed from month 12 onwards, resulting in logMAR decline and recovery not reflected in CaRS-I & II, RHODOS or EAP. In the EAG's base case, idebenone transition probabilities from LEROS were applied to SoC patients from six months onwards as this allowed for the change in logMAR to reflect the SoC treatment effect in the RHODOS and CaRS trials.

In the draft guidance, the committee agreed that LEROS was the more appropriate source to inform idebenone treatment effects and preferred the EAG's approach to derive the SoC treatment effects, given the alignment of the model and clinical outcomes.

In response to the committee's considerations in the DG, the company derived the idebenone and SoC treatment effects using the integrated analysis as described in detail in Section 2.1.2

In the company's base case, the integrated analysis has only been used to inform idebenone treatment effects from six to 36 months, after which time LogMAR is assumed to be fixed. From baseline to six months, the treatment effects are derived from RHODOS, as was assumed in the company's previous base case. The company's approach to deriving a treatment effect over time can therefore be described as follows:

- **Baseline to month 6:** Derived directly from RHODOS.
- **Month 6 to month 12:** Derived from the integrated analysis and with propensity score weights based on stabilised inverse probability of treatment weights.
- **Month 12 to month 36:** Derived from the integrated analysis, weighted and estimated using a logistic regression model with MAR and MNAR assumptions.
- **Month 36 onwards:** No change in logMAR is assumed.

In the company's base case, idebenone and SoC treatment effects have been derived using the logistic MAR model from 12 months; however, scenario analyses were conducted using a weighted MAR and logistic and weighted MNAR models. Mean changes in best BCVA of idebenone compared to SoC from the economic model are presented in Table 11. The company highlights that there is little difference between the treatment effectiveness scenarios in terms of model outcomes.

Table 11. Difference in mean change in best BCVA idebenone vs SoC from model (reproduced from Table 6 in the company's response to DG)

Analysis visit	Difference in mean change in best BCVA idebenone vs SoC from the economic model (LogMAR)* P-value				Difference in mean change in best BCVA idebenone vs SoC from the integrated analysis (LogMAR)
	Logistic model, MAR	Logistic model, MNAR	Weighted observed, MAR	Weighted observed, MNAR	
Baseline	0	0	0	0	-
Month 3	[redacted]	[redacted]	[redacted]	[redacted]	-
Month 6	[redacted]	[redacted]	[redacted]	[redacted]	-
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BCVA, best corrected visual acuity; MAR, missing at random; MNAR, missing not at random; SoC, standard of care

While the integrated analysis provides observations post 36 months, the company assumed that logMAR was fixed from 36 months onwards due to the diminishing number of patient observations from which to inform treatment effects.

3.2.1 EAG critique

The EAG agrees with the company's approach of using the integrated analysis to derive treatment effects for idebenone and SoC but considers that informing treatment effects using RHODOS from baseline to six months is highly inappropriate.

As described in Section 2.2 and presented in Table 10, the RHODOS-derived treatment effects, which utilises [redacted] patient observations compared to the [redacted] observations from the integrated analysis, lead to certain and impossible transition probabilities and health state occupancies of zero within the first year of the model, which the EAG considers is clinically implausible.

At DG clarification the EAG requested the company to derive treatment effects from baseline using the integrated analysis and to include RHODOS in the integrated analysis given its previous exclusions. In response, the company stated that it was impossible to use the integrated analysis to inform the transition probabilities in the first months from baseline, therefore no scenario was conducted. The company stated that the impossibility was because linearity cannot be assumed in the first months due to the non-linear shape of sight deterioration to nadir and then recovery associated with LHON. As the statistical models used to evaluate the outcomes of the integrated analysis are based on a regression model, the lack of linearity means MMRM models cannot be used to derive transition probabilities from baseline to month 12.

The EAG notes that in the company base case, a regression-based approach was not used to calculate the transition probabilities from month six to month 12 using the integrated analysis. Therefore, the EAG considers that patients from the integrated analysis could have been matched at baseline, transition probabilities calculated without a regression model up to 12 months and then a regression-based approach used from 12 months onwards, as has been applied in the company base case. This approach would have allowed for RHODOS patients to be included in the integrated analysis with treatment effects being informed using solely the integrated analysis, rather than

naively using sequentially distinct data sources (the RHODOS data followed by the integrated analysis data) in the model.

As such, the EAG considers that the company's argument for not conducting the scenario using the integrated analysis is flawed and that treatment effects remain a key issue given the company's preference for informing treatment effects from baseline using RHODOS ([redacted] observations) instead of the integrated analysis ([redacted] observations).

Given no scenario was conducted using the integrated analysis to inform treatment effects from baseline, the difference between the company's approach and using the integrated analysis is therefore unknown. However, the EAG notes that if comparing the RHODOS derived six month model outcomes to the trial outcomes, the model appears to overestimate logMAR decline in SoC patients. In the trial, mean change in logMAR from baseline to six months was measured at +0.127 for SoC patients. Comparatively the model estimated an increase in logMAR of +0.31. The EAG notes that this same issue was also raised in the EAG's original report.

At DG clarification the company was asked to explain the difference between the model and trial outcomes given the trial was used to inform the model treatment effects; the company stated that the difference was due to the differences in baseline health state distributions between RHODOS and the integrated analysis. Therefore, when using the RHODOS health state distributions, the treatment effect measured in the RHODOS study are reflected in the model. The EAG notes that when assuming the RHODOS baseline distribution of patients in the model, there is little to no change in the SoC treatment effects, with change in logMAR for SoC patients continuing to be +0.31 in the model compared to +0.127 in the RHODOS trial. As such, the EAG considers that logMAR decline of SoC patients in the model is overestimated and that if RHODOS SoC treatment effects were more closely reflected in the model, the incremental QALYs would be lower, resulting in an increase in the ICER.

In their response to the DG clarification question, the company added that although the early model treatment effects had been informed using RHODOS, they strongly considered that the baseline distribution of patients should be informed using the integrated analysis as the integrated analysis takes into account all available clinical data. The EAG considers that as RHODOS derived treatment effects are applied in the model from baseline to six months, the distribution of patients at baseline

should similarly be informed using RHODOS to better reflect the trial treatment effects. As such, the baseline distribution of patients has been informed using RHODOS in the EAG base case.

When comparing the integrated analysis derived treatment effects to the integrated analysis outcomes, the EAG notes that the idebenone weighted and logistic models provide model outcomes that closely reflect the integrated analysis outcomes. However, the SoC weighted and logistic models fail to provide economic model outcomes that reflect the integrated analysis. Figure 6 presents the changes in logMAR from baseline of the integrated analysis, RHODOS and the model when using treatment effects derived from integrated analysis. For simplicity, as there is little to no difference between the changes in logMAR between the weighted and logistic MAR and MNAR models (Table 11), only the logistic MAR model outcomes have been plotted as they represented the company's base case.

Figure 6. Change in logMAR from baseline

The EAG highlights that the model overestimates the change in logMAR from baseline by approximately 88% (+0.194 compared to +0.103) for SoC patients at month 36 compared to the integrated analysis. This overestimation increases to over 100% if instead assuming the logistic MNAR model (Table 11). Similarly, compared to the results of the integrated analysis without MAR or MNAR assumptions, which most closely aligns with the RHODOS 36-month outcomes, the model overestimates SoC logMAR by approximately 9.22 times (+0.194 vs +0.021). The EAG notes that no scenario was conducted by the company using the integrated analysis weighted model without MAR and MNAR assumptions.

At DG clarification the company was asked to comment on how well the treatment effects derived from the integrated analysis reflected those calculated in the model. In response, the company considered that the economic model accurately reflected the long-term treatment effect of idebenone and SoC, providing Table 12 which they considered to highlight the similarities between the model and integrated analysis outcomes. The company added that in the SoC arm at month 36, there is less than logMAR 0.1 difference between the model outputs and the outputs of the integrated analysis, which clinicians have previously stated to not be clinically significant.

Table 12. Table 4: Change in logMAR from baseline across model outputs and the integrated analysis outputs (reproduced from Table 4 in the company's clarification question response).

Timepoint	Idebenone			SoC		
	Economic model (logistic, MAR)*	Integrated analysis (MMRM, MAR)	Integrated analysis (MMRM, MNAR)	Economic model (logistic, MAR)*	Integrated analysis (MMRM, MAR)	Integrated analysis (MMRM, MNAR)
Month 6	[redacted]	N/A	N/A	[redacted]	N/A	N/A
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Under the company's base-case assumptions
Abbreviations: MAR, missing at random; MNAR, missing not at random

The EAG considers that Table 12 highlights that the economic model closely replicates the idebenone treatment effects from the integrated analysis but underestimates the SoC treatment effects post 18 months; highlighting again that modelled SoC change in logMAR is approximately twice that calculated in the integrated analysis by 36 months. As such, the SoC modelled treatment effects are not just uncertain but are improbable and do not reflect the outcomes of the integrated analysis.

The EAG therefore considers that the company's approach to modelling treatment effects overestimate logMAR decline and underestimate logMAR recovery for SoC patients. Given that logMAR is assumed to be fixed after 36 months, these differences have profound implications to the decision of cost effectiveness, resulting in incremental QALYs greater that one between treatment arms. The EAG considers that if SoC patient sight decline and recovery had been more accurately replicated in the model, the smaller incremental QALYs would lead to a substantial increase in the ICER given the large incremental difference in costs. In the EAG base case, treatment effects post six

months have been estimated using the logistic MAR model as it provided the most conservative difference in treatment effects.

Given the availability of patient data up to 48 months, at DG clarification the EAG requested the company to conduct a scenario using all available patient data. The company conducted the scenario as requested but considered that assuming no change in logMAR from 36 months was more appropriate as only [redacted] observations were recorded at month 42 for both idebenone and SoC arms. The scenario led to a small increase in the ICER, independent of which MRMM model was assumed. In the EAG base case, transition probabilities are included up to 48 months as the four-health state model is assumed, which is considered to make the best use of the limited available data.

Finally, as noted in Section 2.1.4, the EAG highlights that patients were not matched by time since nadir in the integrated analysis. As such, when looking at changes in logMAR over time, compared to SoC patients who appear to reach nadir after approximately 6 to 12 months in the model, idebenone patients only experience logMAR recovery without deterioration to nadir. The EAG is therefore uncertain to how the differences in time since nadir may contribute to the difference in treatment effects given idebenone patient do not appear to experience nadir in the model. However, the EAG notes that patients were matched by time since disease onset. Therefore, the impact of not matching from time since nadir may be mitigated to a certain extent

3.3 Time on treatment

In the previous company base case, idebenone time on treatment was informed using the RHODOS and the EAP study for up to 36 months, with RHODOS and EAP also informing the company's preferred treatment effects. After 36 months, the company assumed that patient logMAR would be fixed and all patients would discontinue treatment. The EAG also preferred to inform time on treatment using RHODOS and EAP; however, the company was critical of the EAG's preferred source of time on treatment as it differed from the EAG preferred source of treatment effects, which was from LEROS. The EAG considered LEROS an inappropriate source to inform time on treatment as patients were discontinued from treatment as part of the study design. Therefore, LEROS time on treatment was unlikely to reflect clinical practice.

In the DG the committee concluded that, "*in clinical practice, people may have idebenone for longer than 3 years and that this would likely be driven by LHON stabilisation*" adding 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)".

As part of their response to the DG, the company explored time on treatment using the integrated analysis. The company noted that there was great variability in the treatment duration across the LHON studies, ranging from LEROS where patients were treated for two years, to the EAP study where patients were treated for over five years. The company therefore explored an analysis looking at the time to *indication* of treatment discontinuation using the integrated analysis dataset. Time to indication for Idebenone discontinuation (months) was defined as the time from first dose to when the treatment should be stopped according to clinical expert opinion. According to the company's clinical experts, patients should be stopped in case of;

- No CRR observed within 24 months;
- A first CRR is observed within 24 months, but no additional CRR observed within 6 months after first CRR;
- A second CRR is observed within 6 months after first CRR, but no additional CRR observed within 6 months after second CRR.

The Kaplin Meier (KM) curve estimating the proportion of patients who discontinue treatment based on the time to indication of treatment discontinuation is presented in Figure 7 and informs the time on treatment calculations in the company's base case.

Figure 7. Time to indication of idebenone discontinuation from the integrated analysis

3.3.1 EAG critique

In response to the DG, the company has preferred to inform time on treatment using time to indication for treatment discontinuation from the integrated analysis. The EAG notes that this approach is highly comparable to treatment discontinuation assumed in the previous company base case with few patients receiving treatment post three years. The EAG considers that this may be due to the time on treatments being limited in the studies included in the integrated analysis. To this point, the EAG notes that idebenone treatment was withdrawn after two years in LEROS, 24 weeks in RHODOS and seven patients continued with idebenone in EAP post 36 months. As such, the EAG considers only the PAROS study did not limit idebenone time on treatment for all patients included in the study.

The EAG notes that in addition to estimating treatment discontinuation using time to *indication* of treatment discontinuation, time to treatment discontinuation was also directly calculated from the integrated analysis, as presented in Figure 8. For clarity, according to the company's SAP, time to indication for idebenone discontinuation was defined as the time from first dose to when the treatment should be stopped according to the company's clinical experts' opinion. Comparatively, time to idebenone discontinuation was defined as the time from first dose to treatment discontinuation.

Figure 8. Time to idebenone discontinuation from the integrated analysis

As presented treatment discontinuation is substantially different to that estimated when including the company's discontinuation indication assumptions, with a significant proportion of patients continuing idebenone treatment post three years. The EAG considers that time to discontinuation from the integrated analysis is more clinically reflective of patient time on treatment as it presents when patients actually discontinued treatment and not when patients should have discontinued treatment according to the company's clinical experts.

As a scenario analysis, the EAG informed time on treatment using time to treatment discontinuation from the integrated analysis which led to an increase in the ICER. Given the EAG's view that time to discontinuation may be more clinically reflective of patient time on treatment, time on treatment has been informed using time to discontinuation from the integrated analysis in the EAG base case.

3.4 Patient HRQoL

In their previous base case, the company preferred to estimate health state utility values using Brown 1990,[9] a time trade off (TTO) study that evaluated the health-related quality of life (HRQoL) of the better seeing eye in 325 patients with visual impairments. Conversely, the EAG preferred to use values from Lawrence *et al.* 2023,[1] which measured HRQoL using EQ-5D in LHON patients.

In the DG, the committee concluded that, "*that Lawrence et al. was a more appropriate source to derive utility values from"* adding that, "[the committee] *would like to see further scenarios explored using varying utility values, in particular for reflecting a counting-fingers health state"*.

In the company's response to DG, the company preferred to use the utility values measured using HUI-3 from Lawrence *et al.*,[1] rather than the ED-5D values. The company considered that the HUI-3 values should be preferred to ED-5D as the HUI-3 includes questions specifically related to vision, thereby more accurately capturing the true burden of visual impairment associated with LHON. The company additionally considered that the HUI-3 results showed the most reflective level of difference in VA, further strengthening the argument for the use of the HUI-3 values. The company also noted that NICE guidelines (DSU TSD 8)[21] states "*evidence from recent reviews suggests that EQ-5D is probably not appropriate for assessing the impact of some specific forms of visual impairment*" and therefore suggested that alternative preference-based measures should be considered instead.

To address the committee's concerns in the draft guidance, the company conducted several scenarios using utilities from Lawrence *et al.* 2023 (EQ-5D-5L and TTO), Brown *et al.* 1999, Czoski-Murray 2009, and Rentz *et al.* 2014.[1, 9-11] Table 13 presents the outcomes of these scenarios.

Table 13. Company HRQoL scenario analyses

Scenario analysis utility source	ICER (£/QALY)
Lawrence *et al.* 2023 – EQ-5D*	40,666
Lawrence *et al.* 2023 – TTO*	34,057
Brown *et al.* 1999	41,544
Czoski-Murray 2009	36,205
Rentz *et al.* 2014	39,470

* - averaged from the UK and ROI population.

Abbreviations: EQ-5D, EuroQol 5 Dimension, ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year; TTO, time trade off.

3.4.1 EAG critique

The EAG considers that the Lawrence *et al.* EQ-5D values are the most appropriate for estimating the LHON utility as, in accordance with the NICE guidelines, EQ-5D is the standard instrument for deriving utility values for QALYs, ensuring uniformity across evaluations. Similarly, the EAG highlights that of the sources of HRQoL utilities in the model, only the Lawrence *et al.* HUI-3 values provided an ICER below a £30,000/QALY willingness to pay threshold.

As relayed to the company in the Factual Accuracy Check (FAC) and also explained in DSU TSD 8, while the DSU does state that, "*EQ-5D is probably not appropriate for assessing the impact of some specific forms of visual impairment"* the next sentence states that, "*unfortunately the evidence to support alternative generic preference-based measures in these populations is also currently limited*". As such, the EAG considers that, "*EQ-5D is assumed to be appropriate unless it is empirically demonstrated not to be the case for a given patient group and its treatment",* as also stated in the DSU TSD 8 guidance. Therefore, the Lawrence *et al.* ED-5D values have been assumed in the EAG base case.

The EAG additionally notes that in the discussion between HUI-3 values preferred by the company in HST 11 and the EQ-5D values preferred by the EAG, "*The committee* [for HST 11] *concluded that the company's HUI3 values lacked face validity. It acknowledged the rationale for the use of HUI3 values and considered that the EQ-5D values were more appropriate because of the potential focus on vision by the clinicians".*

When evaluating the application of the utility values in the economic model, the EAG noted that the standard error (SE) of utilities was the same for each health state, and did not change according to the sources of utility. At DG clarification the company was asked to provide the source of the utility

SEs; the company responded that the SEs were provided in error and instead SEs should be assumed to be 20% of the mean. The company additionally noted that although upper and lower bound confidence intervals are plotted as part of the figures included in the Lawrence *et al.* publication,[1] the actual values are not given. Therefore, assuming SE to be 20% of the mean was appropriate.

The EAG considers that the company's approach to estimating utility SE is inappropriate given the width of the confidence intervals are dependent on the utility, with higher utility health states reflecting higher SEs, which is contrary to what was identified in Lawrence *et al.*, where greater uncertainty was associated with the lower utility logMAR states. However, given the values have not been provided by Lawrence *et al.* the EAG considers that while the approach is not methodologically robust it can be seen as a conservative assumption given idebenone patients are more likely to be in higher utility health states in the model.

3.5 Caregiver HRQoL

In the previous company base case, the company included caregiver disutility for patients with LogMAR >1, with the disutility being derived from Wittenberg *et al.* 2013,[12] aligning with HST 11.[8] In the EAG base case, a caregiver disutility was not applied as evidence from HST11 and the EAG's clinical experts suggested that carer disutility may only be appropriate for children. However, the EAG explored adult carer disutility in a scenario analysis.

In the DG the committee considered 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 company's response to DG, the company stated that caregiver QoL was not collected in the clinical trials for idebenone and the literature on the disutility of caregivers of patients with LHON and other ophthalmology diseases is limited. Hence, the company opted to use caregiver disutilities from Wittenberg *et al.*,[12] as was applied in HST 11 for patients with logMAR >1.[8]

The company noted that in the EAG report, the EAG stated that the HST 11 committee, "*considered 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".* The company therefore considers that the EAG of HST 11 agrees with the company approach as this was the approach used in their base case.[8] As such the

company considered it imperative to include caregiver disutility in the base case for child and adult patients with a logMAR>1.

3.5.1 EAG critique

The EAG agrees with the company that the EAG of HST 11 considered that it was only appropriate to apply carer disutility for parents of children with a condition that causes blindness, leading to the EAG of HST 11 removing carer disutility for adults in their base case. Therefore in the case of LHON, where disease on-set is approximately early adulthood, the EAG considers that it is inappropriate to apply a carer disutility to LHON patients.

The EAG notes that when explored probabilistically the application of carer disutility can often lead to a health state utilities of zero, due to the SE of the disutility being three times that of the disutility itself (SE of 0.12 vs disutility of 0.004). Additionally, separate carer disutilities have been applied for each model health state, leading to incidences where carer disutility for a worse logMAR health state could be less than better LogMAR health states in the probabilistic analysis, which the EAG considers to be implausible.

At DG clarification, the company was requested to provide the source of the disutility, given that carer disutility SE was the same as health state utility SE (0.12), and to conduct a scenario where the same care disutility was applied to logMAR>1 health states. The company stated that the carer disutility SE had been provided in error and that SE should instead be assumed to be 20% (0.2) of the mean value. The company conducted the scenario as requested, which had a minimal impact on the ICER.

Overall, the EAG considers that it is inappropriate to include carer disutility for LHON patients, given the opinions of the EAG's clinical experts and the conclusions of the EAG and committee from HST 11. As such, carer disutility is not included in the EAG base case.

3.6 Health state resource use

In the previous company base case, the health state resources included in the economic model were informed using Meads *et al.* 2003,[2] a cost study including 28 patients with age-related macular degeneration (AMD) and an average age of 65. In the company base case, the frequencies of these resources were estimated using the difference in frequencies between Meads *et al.* and the company's clinical expert opinions.

The EAG considered that the health state resources included in the model were appropriate but preferred to apply resource costs only to patients with a logMAR>1, except depression costs which were applied for all health states. This assumption was informed by the EAG's clinical experts who advised that they, "*would not expect young people with vision equal to driving vision to fall regularly*" and, "*in clinical practice, people who would incur health care resources would be clinically visually impaired with a logMAR of 1 to 1.3*". Additionally, the EAG preferred to apply outpatient care and supportive living costs as one-off costs as this aligned with the feedback provided from the EAG clinical experts.

In the DG, the committee stated that, "*although there were significant differences in the approaches used by the company and the EAG regarding the use of health-state resource utilisation, this had a minor impact on the cost-effectiveness results".* Overall, committee concluded that, "*it was appropriate to apply the resource costs of outpatient visits (obtaining low vision aids and rehabilitation) for health stages with a LogMAR of less than 1"*.

Post DG, the company was informed by their clinical experts that there is no longer a blind registration fee to patients, that supportive living costs should occur over a lifetime horizon, and that they would expect costs associated with depression to occur over a much longer period of time.

Therefore, to address the EAG and committee's concerns and incorporate the company's clinical expert feedback, the company conducted two scenario analyses:

- *Scenario 1:* Health care frequencies calculated using the midpoint estimates between the company's clinical expert survey and Meads *et al.* and applying all resource use inputs for all health states.
- *Scenario 2:* Healthcare frequencies informed using solely the company's clinical expert survey, and applying hospitalisation, depression and outpatient care costs for all health states. For all other costs, resources were only applied to patients with LogMAR>1.

Applying scenario 2 to the company's updated base-case resulted in a decrease of the ICER from £28,451 to £27,134,

3.6.1 EAG critique

Between the two scenarios provided by the company, the EAG considers scenario 2 to be the more appropriate given it takes into account the committee's preferences from the DG. However, the EAG

notes that the frequencies assumed by the company's clinical experts are over double those recorded in Meads *et al.* [2] As such, the EAG considers that the frequencies from Meads *et al.* should be assumed, given that the mean age of LHON patients in the integrated analysis is less than half the age of patients in Meads *et al.* with AMD. [2] As such, health care resource use frequencies have been informed using only Meads *et al.* in the EAG base case.

With respect to the company's preference of applying supportive living costs over a lifetime, the EAG notes that the cost of supportive living from Meads *et al.* was assumed to reflect the cost of a community home care worker. [2] A clinical expert advising the EAG noted that they expected this would entail assessing the home environment and installing features that may help, noting that this would generally be a one-off visit rather than a regular on-going cost. The EAG therefore continues to assume that supportive living costs should be applied as a one-off cost in the EAG base case.

The EAG additionally notes that in the company's response to the DG, the company's clinical experts stated that, "*whilst the current resource use estimates are plausible, they would expect to see an approximate times two increase in outpatient care resource use due to the low number of vision clinics. The reason for the increase was the fact that with no treatment available there is little value to be gained from a clinic visit, therefore with the introduction of idebenone an increase is to be expected"*. To an extent, the EAG agrees with the company's clinical experts that SoC patients would have little to gain from a clinical visit given regular ophthalmologist are already included in the model. The EAG therefore requested the company to conduct a scenario where SoC patients were assumed to require less or no additional outpatient care compared to idebenone patients. The company conducted the scenario as requested, which led to a minor increase in the ICER. The company's clinical experts' assumption that SoC patients will require half the number of idebenone patients' outpatient visits informs the EAG base case.

The EAG notes that in the model, health state costs per cycle are calculated as a product of health state resource use frequencies and their respective costs. In the PSA, both frequencies and costs are varied probabilistically in the model using the company's assumed SE of 20%; however, the health state cost per cycle calculated from their product is also varied probabilistically. The EAG considers that as the frequencies and cost uncertainties have already been accounted for in the PSA it is inappropriate to account for an additional uncertainty around the calculated cost per cycle. At clarification the company was asked to justify their approach; the company thanked the EAG for identifying the double counting of the uncertainty and conducted a scenario in which only the SE of

the cost and frequency of healthcare resource use which led to a minor increase in the probabilistic ICER. In the EAG base case, the resource use and costs are varied probabilistically and not the resulting cost per cycle.

3.7 Transition probabilities in the PSA

In the previous company base case, the company did not vary transition probabilities in the probabilistic sensitivity analysis (PSA) but only the baseline distribution of patients across health states. The EAG considered the inability of the PSA to account for the treatment effectiveness uncertainty a key issue, given the highly uncertain treatment effects.

To address this concern, in their response to the draft guidance the company built into the model the capability to allow transition probabilities to vary probabilistically. In their base case, the company uses the transition probability SE values from the integrated analysis (logistic MAR model) for month 12 to month 36 and applies them to all other transition probabilities derived from the integrated analysis (weighted and NMAR models). For the SEs of transition probabilities from baseline to month 12, an average SE value was calculated from the existing SEs and applied.

The results of the PSA using the company's updated base case assumptions are provided in Section 3.2.

3.7.1 EAG critique

The EAG is concerned with the company's approach to accounting for the treatment effectiveness uncertainty as the RHODOS- and integrated analysis-derived treatment effectiveness estimates are uncertain and these uncertainties do not appear to be accurately reflected within the PSA.

With respect to the RHODOS-derived transition probabilities, as previously described, due to the small number of patients in the RHODOS trial, some transition probabilities are only informed by a single observation, which effectively leads to unrealistic transitions that are guaranteed to occur. While the EAG considers these transitions to highly uncertain, given they are estimated using a single observation, the SE of these transition probabilities is assumed to be 0.011 in the company's base case. As such, there is very little variation in these transitions with many transitions continuing to be implausibly likely. These transitions are highly impactful to the model, particularly for SoC patients, as they lead to all logMAR <0.3 patients progressing to the logMAR 1.3–1.7 health state in the first cycle of the model.

On investigation into how the RHODOS transition probability SEs have been estimated, the EAG notes that for both RHODOS and integrated analysis derived transition probabilities, the company has calculated the SEs for these transitions as the product of the transition probability and a value termed the "transition variation parameter". This parameter was calculated as the mean SE from the logistic MAR model transition probability SEs from months 15 to 18. That is to say, all transition probabilities SEs in the model are informed using the logistic MAR model, independent of the source of the treatment effectiveness. In the company's base case, the transition variation parameter is a fixed value of 0.011.

As the transition probability SE for the weighted and MNAR models are calculated as the product of the transition probability and the transition variation parameter, the greater the proportion of patients transitioning between health states, the higher the calculated SE, with the greatest SE possible being 0.011 for a transition probability of 100%, and 0.55 for a transition probability of 50%.

At clarification the company was asked to justify their approach; the company responded that the transition probabilities from RHODOS were calculated based on patient-level data and patient counts, therefore, SEs were not calculated for the transition from baseline to month six. For transition probabilities from six to 12 months and the weighted observed data, no SE data were available to inform these transitions. A such the company made the simplistic approach of taking the average SE value from the logistic model and applying it to the weighted model. However, for logMAR MAR transition probabilities from months 12 to 36, SEs were derived alongside the probabilities. The EAG therefore considers that while the company's approach has been explained, it remains unjustified and is conceptually flawed.

In order to explore the impact of the transition probability SEs on the decision of cost effectiveness, the company conducted two additional scenarios. In one, a SE of 20% was applied to the transition probabilities from baseline to month 12, in another a SE of 20% was applied to all transitions. The company noted that the scenarios had a minimal impact on the ICER. The EAG notes that in these scenarios, due to how transition probabilities have been calculated, the 20% SE only applied to transition probabilities where patients transitioned from a single to multiple health states. As such, transition probabilities of 100% did not change, with the scenarios continuing to result in clinically improbably health state occupancies.

With respect to the integrated analysis, the EAG notes that treatment effects were highly uncertain, with the difference in treatment effects approaching zero and no significant difference in treatment effects measured at month 36. Comparatively, the logistic model SEs that are applied to all transition probabilities are highly conserved, which the EAG considers to lack face validity. Noting that patient observations were imputed in the logistic MAR model, the EAG was concerned that the small SEs may in part be due to the patient observations being heavily imputed, leading to an inflated sample sizes and smaller SEs. As only the proportions of patients transitioning through the model were provided and not the number of patients from which the SEs had been derived, at DG clarification the company was asked to provide the proportion of observations that had been imputed in the logistic MAR model across all timepoints. In the company's response, the proportions of imputed observations were not provided. As such, the EAG considers that logistic MAR SEs may not be reflective of the treatment effectiveness measured in the integrated analysis due to the patient observations being highly imputed.

Overall, the EAG considers that the company's methods for varying treatment effects according to the uncertainty are flawed, leading to an underestimation of treatment effect uncertainties in the model.

4 Company cost effectiveness analysis and results

4.1 Company's cost effectiveness results

Table 14 presents the company's updated deterministic and probabilistic base case results. Probabilistic results were collated from 1,000 probabilistic model iterations generated using a Monte Carlo simulation.

Table 14. Company base case results

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28,451
Probabilistic results							
SoC	[redacted]	-	[redacted]	-	-	-	-
Idebenone	[redacted]	-	[redacted]	[redacted]	-	[redacted]	29,311

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

Figure 9 presents a scatterplot of the probabilistic iterations, with a cost-effectiveness acceptability curve (CEAC) also presented in Figure 10. From these analyses, the probability that idebenone is cost-effective versus SoC was found to be 58% at a willingness to pay (WTP) threshold of £30,000.

Figure 9. Monte Carlo iterations scatter plot, company base case

Figure 10. Cost-effectiveness acceptability curve

4.2 Company's sensitivity analysis

The company conducted a one-way sensitivity analysis (OWSA) to assess the sensitivity of the ICER to isolated parameter uncertainty (Figure 11).

Figure 11. One-way sensitivity analysis

4.3 Company's scenario analyses

The company undertook a series of scenario analyses to assess the impact of alternative modelling assumptions on the ICER. Scenario results using the eight-state model are presented in Table 15, with results assuming the four-state model in Table 16.

Table 15: 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]	28,451
Clinical inputs - Integrated data	1	Logistic model, MAR (in both treatment arms)	Logistic model, MNAR (in both treatment arms)	[redacted]	[redacted]	25,378
	2		Weighted observed, MAR (in both treatment arms)	[redacted]	[redacted]	28,735
	3		Weighted observed, MNAR (in both treatment arms)	[redacted]	[redacted]	25,908
Utility source	4	Lawrence *et al.* 2023 – HUI*	Lawrence *et al.* 2023 – EQ-5D-5L*	[redacted]	[redacted]	40,666
	5		Lawrence *et al.* 2023 – TTO*	[redacted]	[redacted]	34,057
	6		Brown *et al.* 1999	[redacted]	[redacted]	41,544
	7		Czoski-Murray 2009	[redacted]	[redacted]	36,205
	8		Rentz *et al.* 2014	[redacted]	[redacted]	39,470
Resource use source	9	Scenario 1: Midpoint values of KOL survey and Meads *et al.* 2003	KOL survey	[redacted]	[redacted]	27,604
	10		Meads *et al.* 2003	[redacted]	[redacted]	29,299
	11		Scenario 2: KOL survey (alternative scenario at DGC)	[redacted]	[redacted]	27,134
Resource use costs	12	Blind registration cost of £0	Blind registration cost of £165	[redacted]	[redacted]	28,439
	13	Depression costs applied for 2 years	1 year	[redacted]	[redacted]	28,461
	14		Lifetime	[redacted]	[redacted]	28,234

* - averaged from the UK and ROI population.

Abbreviations: HUI, Health utilities index; ICER - Incremental cost-effectiveness ratio; MAR, Missing at random; MNAR, Missing not at random; PAS - Patient access scheme; QALY-Quality-adjusted life years; ROI, Republic of Ireland; TTO, Time trade off; UK, United Kingdom

Table 16: Scenario analysis (revised company base-case, [redacted]) – EAG's preferred 4 health state structure

Parameter	Scenario number	Base-case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)
Base-case				[redacted]	[redacted]	32,698
Clinical inputs - Integrated data	1	Logistic model, MAR (in both treatment arms)	Logistic model, MNAR (in both treatment arms)	[redacted]	[redacted]	28,369
	2		Weighted observed, MAR (in both treatment arms)	[redacted]	[redacted]	32,627
	3		Weighted observed, MNAR (in both treatment arms)	[redacted]	[redacted]	28,345

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

5 EAG cost effectiveness analysis and results

5.1 EAG scenario analysis

In Section 2 of this report, the EAG has described several scenarios which warranted further exploration, in addition to the company's own sensitivity and scenario analyses. These scenarios and their outcomes are presented in Table 17.

Table 17. Results of the EAG's scenario analyses

	Results per patient	Comparator	Intervention	Incremental value
-	Company base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	28,451
1	Informing time on treatment using time to discontinuation from the integrated analysis			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	54,793
2	Applying outpatient resource use to logMAR <1 health states using Meads *et al.*			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	28,456

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

5.2 EAG preferred assumptions and results

Listed below are the EAG's preferred assumptions, with the independent and cumulative ICERs provided in Table 18. The inclusion of these assumptions results in the EAG's deterministic and probabilistic base case cost-effectiveness results, as presented in Table 19.

- Four health state model;
- RHODOS used to inform the distribution of patients at baseline;
- Transition probabilities applied up to 48 months;
- Time on treatment informed using the Integrated analysis time to discontinuation;
- Health state utilities informed using Lawrence *et al.* ED-5Q values;[1]
- Carer disutility not included;

- Using only Meads *et al.* to inform health care resource use;[2]
- Outpatient resource use from Meads applied to logMAR<1 health states;
- Supportive living applied as a one-off cost;
- SoC patients assumed to require half the number of idebenone outpatient visits.

Table 18. EAG preferred modelling assumptions

Preferred assumption	Section in EAG report	Independent ICER (£/QALY)	Cumulative ICER (£/QALY)
Company base case	-	28,451	-
Four health state model	2.2	32,698	32,698
RHODOS baseline distribution of patients	2.3	28,864	33,226
Transition probabilities up to 48 months	2.3	29,387	34,134
Integrated analysis – time to discontinuation	2.4	54,793	65,608
Lawrence *et al.* EQ-5D values[1]	2.5	40,666	89,632
No carer disutility	2.6	31,118	101,497
Meads *et al.* health care resource use[2]	2.7	29,299	103,416
Outpatient resource use applied to <1 logMAR health states*	2.7	29,310	103,436
Supportive living applied as one-off cost	2.7	31,349	104,388
SoC patients require half idebenone outpatient visits	2.7	28,506	104,442

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

*Previous assumption included

Table 19. EAG base case results

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	104,442
Probabilistic results							
SoC	[redacted]	-	[redacted]	-	-	-	-
Idebenone	[redacted]	-	[redacted]	[redacted]	-	[redacted]	108,376

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

Figure 12 presents a scatter plot of the model iterations used to inform the EAG's probabilistic base case. While a CEAC has not been provided, the probability of idebenone being cost-effective assuming a willingness to pay threshold of £20,000 or £30,000 was 0%.

Figure 12. Monte Carlo iterations scatter plot, EAG base case

5.3 EAG sensitivity analysis

Figure 13 presents the EAG base case one-way sensitivity analysis which includes the 10 parameters the ICER was most sensitive to. Similar to the one-way sensitivity analysis conducted with the company's preferred assumptions the model was model sensitivity to patients utility, with the ICER sharply increasing when utility values between the logMAR<0.3 and logMAR 0.3–0.6 health states were most similar.

Figure 13. One-way sensitivity analysis, EAG base case

5.4 Conclusion of cost-effectiveness

Overall, the EAG considers that costs have been adequately estimated in the model when assuming the Meads *et al.* health state resource use and time to discontinuation from the integrated analysis, without the company's clinical experts' additional assumptions. However, the health outcomes remain highly uncertain and underestimated in the case of the modelled SoC treatment effects, derived from RHODOS and the integrated analysis.

The EAG considers that the inaccurate estimate of the SoC treatment effect is primarily driven by the company choosing to apply the RHODOS and integrated analysis treatment effects in naive succession rather than including RHODOS in the integrated analysis and deriving treatment effects from a coherent data set. The outcome of this approach is that the model outcomes fail to reflect the integrated analysis or RHODOS trial, with the model overestimating logMAR decline and underestimating logMAR recovery for SoC patients.

The EAG considers that should the model outcomes more accurately reflect the RHODOS and the integrated analysis outcomes, the incremental QALYs would decrease and incremental costs increase, leading to a substantial increase in the ICER, given the high incremental costs. The EAG notes that a similar conclusion was drawn by the EAG in the original EAG report, with SoC logMAR decline and recovery also misaligning with the trial data, leading to the incremental QALYs being overestimated and the EAG base case being an underestimate.

Due to the underestimation of the SoC treatment effect in any of the company's and EAG's analyses, the EAG's base case ICER is also an underestimated. Had the SoC treatment effect had been estimated more appropriately, the EAG ICER would likely be considerably higher.

With respect to treatment effectiveness uncertainty, the EAG considers that the company's methods are fundamentally and conceptually flawed, leading to highly constrained probabilistic treatment effects. The integrated analysis highlights the similarity in treatment effects for idebenone and SoC, with the confidence intervals approaching zero across all time points and including zero at 36 months, this uncertainty is not captured in the model.

When considering the eight-state model preferred by the company, the EAG considers that had the integrated analysis been used to derive treatment effects from baseline (using the [redacted] possible observations instead of the [redacted] from RHODOS), the transitions of the eight-state model may have been informed by a sufficiently large sample of observations, leading to the eight-state model being appropriate for decision making. However, as RHODOS has been used to derive treatment effects from baseline to six months, leading to key transition probabilities being informed by single observations and health state occupancies of zero after a single model cycle, the EAG considers that the four-health state model makes the best use of the limited available data from RHODOS. Should the company have provided the scenario requested by the EAG in which the off-chart health states of the four-health state model were separated, this requested model structure would have been preferred in the EAG base case.

Finally, aside from treatment discontinuation, the ICER was found to be most sensitive to the source of health state utilities. While the company has preferred the utilities measured using HUI-3 from Lawrence *at al.*,[1] the EAG considers that the EQ-5D Lawrence *et al.* values should be preferred given that EQ-5D is the standard instrument for deriving utility values for QALYs in NICE technology appraisals. The EAG notes that the same considerations between HUI-3 and EQ-5D values were discussed in HST 11, with the committee considering that the EQ-5D utilities were most appropriate.[8]

6 References

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

Dear EAG,

We wish to comment specifically on a number of areas within the EAG Critique (issued in response to Chiesi's updated submission – submitted to NICE Docs on 15th November 2024).

Considerations Regarding Appropriateness of Including RHODOS RCT Patient Level Data into The Integrated Analysis

When the aim is to evaluate the intended effect of an intervention, the randomized clinical trial (RCT) is the gold standard [1]. Evidence generated by a RCT is in the high-level hierarchy of the evidence generated method. Randomization prevents selection bias and insures against accidental bias. It produces comparable groups and eliminates the source of bias in treatment assignments [2]. Blinding is a critical methodologic feature of RCTs, that reduces performance and ascertainment bias after randomization. For all the above reasons, the RHODOS data, covering (as per study design) the first 6 months from baseline, have been used to estimate TPs and clinical efficacy (as per RHODOS CSR) in preference to the integrated analysis for the first 6 months. Integration of RCTs data at patient level with the other interventional and non-interventional studies in this period would ignore the inevitable clinical and methodological heterogeneity between RCTs and observational studies [3]. Making use of the best available evidence, transition probabilities (TPs) after 6 months have been estimated considering the integrated data.

Considerations Regarding Propensity Score Weights Approach

All the analyses on the integrated data has been performed weighted, by propensity score weights. This guarantees obtaining estimates of relative treatment effect of idebenone vs SOC that are unbiased by different distributions of prognostic factors (an issue that is not present in RHODOS, being a RCT free from bias as per design, as stated above). Each patient is maintained in the analysis, but with a proper weight, thus controlling the distribution of the prognostic factors. whilst still including the same minimum and maximum values of the unweighted distribution (the patients are not excluded but have a lesser weight in the analysis).

Aligning baseline characteristics of the integrated analysis to those of patients from RHODOS was not appropriate, since the granular (i.e., at patient level) integration of RHODOS data has not occurred. There are multiple reasons for not integrating the RHODOS data and these are reported through this document.

Considerations Regarding Linearity and Modelling Approach

The clinical efficacy after 12 months has been evaluated using the integrated analysis. There is a broad consensus on the need to treat patients for more than 12 months, hence our decision to evaluate clinical efficacy from 12 months.

This decision made it possible to apply inferential techniques based on linear methods. In the natural history of LHON, after onset, disease progression is expected to be characterised by a quick deterioration until the 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, but it's clinically reasonable after 12 months from baseline. In the first months after baseline, a nonlinear modelling approach would not be possible, since, while the average shape of the visual acuity might be postulated starting from the onset, the collection of the data is starting from baseline.

Hence, given the heterogeneity of patients in their time at baseline from onset, itis impossible to postulate a mathematical function for a nonlinear model fitting too (The nonlinear function f (x, ij i β) models the relationship between the response variable yij and the explanatory variable x) [4].

Indeed, the lack of a mathematical function to model the visual acuity in the period of non-linearity is complicating the statistical analysis options.

Considerations Regarding Primary Analysis

In our primary analysis a Mixed Model for Repeated Measure (MMRM) has been applied. MMRM are becoming the benchmark to analyse normally distributed longitudinal responses [5]. They use a log-likelihood function in order to estimate parameters of a probability distribution that maximises the likelihood of having generated the observed data. The method makes use of all available data, including patients with partial data (i.e., with missing values at some time points) in order to arrive at an estimate of the mean treatment effect without filling in missing items.

This is made possible by modelling longitudinal relationships (covariances) between data across all the time points based on observed data and then using these longitudinal relationships for inference about the mean treatment effect at the final time point over all patients regardless of whether they had observed data at that time point or not [6]. The MMRM approach appears to be a better choice in maintaining statistical properties of a test as compared to the multiple imputation (MI) approach for the above-mentioned reasons [7].

Considerations Regarding Sensitivity Analysis

In order to assess the impact of the assumptions about missing data on our conclusion, we performed a sensitivity analysis using multiple imputation (MI), exploring two different scenarios, i.e. missing at random (MAR) and missing not at random (MNAR).

Both have been presented as it is not possible to test MAR versus MNAR as the information that is needed for such a test is missing [8] (or at least there is no consensus on whether and how this can be tested).

Using MI in a MAR setting is usually said to be a standard MI. Standard MI and MMRM approaches belong to the same class of analysis methods in terms of their basic assumptions regarding the missingness mechanism, both assume that unobserved outcomes of patients who discontinued do **not** systematically differ from observed outcomes of patients who remained in the study, provided that we account for relevant observed factors prior to discontinuation in our statistical model.

In the MMRM and regression MI model all the collected prognostic factors have been included. The stage of disease has been included too, by the simultaneous inclusion of time from onset and visual acuity at baseline. The same factors have been included in the propensity score weights computation, guaranteeing a proper balance of the samples. Visual acuity at nadir is an important potential prognostic factor, but will most likely be biased as explained below:

- For idebenone patients, not all the studies allowed retrospective collection of data: this implies that for all those patients with data after months from the onset, the nadir is likely to be missed, while for those with a more recent onset, the nadir value will be while the patient is being treated
- For SOC patients, although the registry studies foresaw the collection of retrospective data, the schedule of the visits is arbitrary (being a non-interventional study). This can bias the nadir values based on disease severity, the actual timepoint of nadir may not have been collected.

The MNAR approach has been also explored. As per O'Kelly *et all* (2014), the idea of the sensitivity analysis is not to test a range of assumptions, in order to find the assumption about missing data that is the best fit. Since we do not have the missing data, we will never know what assumption is nearest the truth [6]. The purpose is to assess how results are dependent on the primary assumptions on missing data.

The implied question answered by sensitivity analyses should be "If we take a clinical view of what happens to withdrawals that is plausibly unfavourable to the experimental arm, is the conclusion from the primary statistical test still credible?" [6].

In the MNAR assumption, idebenone patients have been imposed to follow a SOC distribution as if no longer under observation. This is a strong, biased, unfavourable assumption, also questionable from a clinical point of view. However, the results, in terms of relative clinical efficacy, have been confirmed. The results of both imputations cannot be taken into account by single arm. They need to be read in conjunction.

As detailed above, the MMRM without implicit imputation, takes into consideration the longitudinal correlation and covariation that reduce the variability and possibly creates the shape of log-likelihood that is different from those generated using imputed values. But this is common for both the treatment arms, hence estimates of the relative treatment effect are unbiased. The purpose of the sensitivity analysis by MI was to check the MAR vs MNAR assumption. Since the results of the two approaches perfectly match, both in terms of treatment effect and relative treatment effect, we conclude that missing data is not impacting the results.

For the period from 12 months onwards, the MI MAR and MNAR datasets have been utilized to estimate TPs without any change to the model described above. While, for the period 6 to 12 months, number and percentage of patients transitioning from one health state to the other have been computed with no assumptions and no imputation but considering the PSW to balance prognostic factors.

Considerations Regarding Utilising Different Data Sources in the Economic model

At every timepoint of the model, the best possible data sources are used to ensure that the clinical benefit of idebenone is accurately captured compared to SoC. This means using the:

- pooled baseline distribution from the integrated analysis, including RHODOS, as agreed by with clinical experts,
- the only head-to-head RCT for idebenone versus placebo (RHODOS) from baseline to 6 months
- then supplementing the long-term modelling with data from the integrated analysis from 6 months onwards.

As described above, we maintain the position that the RHODOS RCT should solely be used to inform the first 6 months of the TPs in the economic model as there is a strong preference for using high-quality RCTs as the basis for the cost-effectiveness analysis. It is neither clinically nor methodologically appropriate to combine the RCT data of RHODOS with real-world evidence used in the integrated analysis. However, the TPs obtained from RHODOS have been applied to the baseline distribution from the integrated analysis, to utilise the best available sources and improve the generalizability of RHODOS results in the economic model.

Given the combination of data sources in the economic model, the results from the economic model may not be fully aligned with clinical results at every timepoint from a single source, such as RHODOS at 6 months or the integrated analysis at 36 months, which explains the differences described in Figure 6 of the EAG report. However, we maintain that this approach is using all available clinical data in the best possible way.

We hope this additional detail has been helpful in aiding the EAG in their interpretation of our analyses and can support in ensuring a timely recommendation of idebenone to patients who are suffering from this severe and debilitating disease.

Kind Regards,

[redacted]

[redacted], Chiesi Ltd

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Idebenone Start/Stop Treatment Criteria

All patients with a confirmed diagnosis of LHON to be offered treatment with idebenone, subject to the following criteria:

Patients to have visual acuity (VA) assessment at least every 6 months.

Clinical recovery will be assessed by VA according to the following.

- Clinically relevant recovery (CRR) relative to the worst recorded VA (the nadir) and defined as:
    - Either moving from off-chart to on-chart by at least 5 letters (1 line)
    - Or an improvement on-chart of at least 10 letters (2 lines)

1. All patients will stay on treatment for a minimum of 24 months if there are no issues with tolerability.
2. Patients who have not experienced a CRR within 24 months will then stop treatment.
3. Patients who experience a CRR will stay on treatment until the improvement has plateaued for 2 successive periods (i.e. no further improvement in VA at the following visit) up to a maximum treatment duration of 36 months.

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

31st January 2025

Dear EAG,

The company has identified an error in an analysis conducted by the EAG within their critique of the company's response to the draft guidance and, given the impact it has on the interpretation of the robustness and suitability of the company's economic model, would like to clarify it prior to the second Committee Appraisal Meeting.

As stated on page 31 of the EAG critique of the draft guidance response, the company clarified that the difference between the outcomes in the model and the outcomes of the clinical trial/integrated analysis (measured as the change in logMAR; see Figure 6 of the EAG's critique of the Company's draft guidance (DG) response) was due to the differences in baseline distributions between RHODOS and the integrated analysis. Therefore, when using the RHODOS health state distribution, the treatment effect measured in the RHODOS study are accurately reflected in the model.

The EAG commented that "*when assuming the RHODOS baseline distribution of patients in the model, there is little to no change in the SoC treatment effects, with change in logMAR for SoC patients continuing to be +0.31 in the model compared to +0.127 in the RHODOS trial.*".

However, the company would like to note that after reviewing the EAG's model, the EAG seems to be applying the RHODOS only baseline *characteristics* and not the RHODOS only baseline *distribution*, hence why there is little to no change in the standard of care (SoC) treatment effects at month 6 and consequently after 6 months.

In order to apply the RHODOS only baseline distribution in the economic model, the number of patients starting in each health state needs to be updated to RHODOS only values in Sheet "Data store", cells W12:W19. The RHODOS only values can be found in "Data store", cells D12:D19. The change in logMAR was calculated based on the distribution of patients in each health state provided in Sheet "Results", cells E99:K120 multiplied by the logMAR midpoint of each health state range (e.g logMAR 0.45 for the logMAR 0.3-0.6 health state).

In order to provide further clarification on this issue and to explain the differences shown in Figure 6 of the EAG's critique, the company has provided revised plot of the model outcomes compared with the clinical trial outcomes for the first 6 months using the RHODOS only baseline distribution. This has been presented for both the idebenone and SoC treatment arms and both the company's eight health-state model structure and the EAG's four health-state model structure in Figure 1 and Figure 2, respectively.

As demonstrated in Figure 1, when considering the data from RHODOS RCT only and the eight-health state structure, the outputs of the model closely align with the outputs of the RHODOS clinical trial in both treatment arms. The change in logMAR at 6 months from the economic model is +0.117 compared to +0.127 as seen in RHODOS in the SoC arm. This alignment is also replicated in the idebenone arm, with a change in logMAR at 6 months of -0.065 compared to -0.048 as seen in RHODOS RCT. For reference a difference of 0.02 in logMAR is equivalent to 1 letter on a ETDRS scale.

However, the same conclusion cannot be made regarding the EAG's four-health state structure for the SoC and idebenone treatment arms (see Figure 2), specifically, with the model underestimating the change in logMAR at 6 months in the SoC arm by ~60% and overestimating the change in logMAR at 6 months in the idebenone arm by ~35% . This further demonstrates how clinically inappropriate the four-state model structure is in capturing the true value of idebenone.

Figure 1: Change in logMAR from baseline to 6 months using RHODOS only baseline distribution in the company's eight health-state model structure

Abbreviations: SoC – Standard of Care

Figure 2: Change in logMAR from baseline to 6 months using RHODOS only baseline distribution in the EAG's four health-state model structure

Abbreviations: SoC – Standard of Care

In order to provide further clarification on the differences presented in Figure 6 and the EAG's critique, the company have carried out a similar exercise as above but using only the integrated analysis data source for the baseline distribution and transition probabilities from 12 months onwards. The company focused on SoC population only, as this is where EAG concerns were.

In this analysis, the baseline distribution from the SET 2, non-imputed, weighted population from the integrated analysis (SoC) was applied, transition probabilities between 0-12 months were completely excluded, distribution between health states at 12 months from the integrated analysis were applied and the integrated analysis transition probabilities (logistic model, MAR) from month 12 onwards were applied. This plot is presented in Figure 3.

As demonstrated, the outputs of the economic model align with the outputs of the integrated analysis across all timepoints which demonstrates that the model is robust and accurately estimates the clinical effectiveness.

Figure 3: Change in logMAR from baseline using data from the integrated analysis only from 12 months onwards in the company's 8-health state structure

Abbreviations: SoC – Standard of Care

These two exercises confirm that the 8-health state economic model is robust and accurately reflects clinical data when only one source is used to populate both: the baseline distribution between health states and transition probabilities.

If the combination of sources is used in the economic model, the outputs from the model may not be fully aligned with outputs from a single source (either RHODOS or integrated analysis).

The company maintain the use of the best possible source at every timepoint in the model:

- Baseline distribution: integrated analysis
    - This is the largest possible sample size of patients and the most reflective of clinical practice.
- Transition probabilities from baseline to 6 months: RHODOS
    - As the only head-to-head RCT comparing idebenone to placebo
- Transition probabilities after 6 months: integrated analysis

Th company hope that this can support the EAG in their evaluation and the committee in their decision making in order to assure a timely recommendation for idebenone for patients with LHON.

Kind Regards.

[redacted]

[redacted], Chiesi Ltd

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

EAG response to the company's letters, post draft guidance

Source of funding

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1 Introduction

The EAG (external assessment group) outlines in Section 2 of this report their response to the company's letters addressing their considerations of the EAG's critique of the company's draft guidance response and a factual inaccuracy identified in the same critique. In addition to the EAG's response, the EAG provides in Section 3 an updated EAG base case, following the company's identification of a factual inaccuracy.

2 EAG response

2.1 Considerations Regarding Appropriateness of Including RHODOS RCT Patient Level Data into the Integrated Analysis

The EAG appreciates the company's rationale for not integrating RCT data with other interventional and non-interventional observational studies due to methodological heterogeneity but is concerned about the mismatch between the populations informing the 6-month data and subsequent follow-up data. That is, the integrated analysis population used for the longer-follow up data was not matched with the RHODOS RCT population used for analyses up to 6-months. Therefore, the EAG's concerns over the appropriateness of applying the RHODOS RCT and integrated analysis treatment effects separately in succession in the economic model, naively assuming that the two data sets are coherent, remain. The EAG requested the results of the integrated analysis for up to 6 months to allow for a comparison between these treatment effect estimates and those of the RHODOS RCT, but the company did not provide these results. Thus, the EAG could not assess whether the 6-month results of the RHODOS trial aligned with the 6-month results of the integrated analysis or whether the economic model reflected the company's integrated analysis.

2.2 Considerations Regarding Propensity Score Weights Approach

The EAG had not raised concerns about the company's propensity score weights approach. However, the EAG considers that aligning the baseline characteristics of patients in the integrated analysis with those of the RHODOS RCT, as opposed to aligning the baseline characteristics of the idebenone and standard of care (SoC) patient groups within the integrated analysis, would have been more appropriate. This would have ensured that the population informing the first 6 months of the model (RHODOS) was coherent with the subsequent data from the integrated analysis, which informs the model after 6 months. The EAG considers the company's "unmatched" or "naive" approach to be a major limitation of the model and introduces potentially avoidable uncertainty in the model's results.

The EAG notes that aligning the baseline characteristics of the integrated analysis to those of patients from RHODOS would have been an alternative approach the company could have considered if they did not want to include RHODOS in the integrated analysis.

2.3 Considerations Regarding Linearity and Modelling Approach

The EAG agrees with the company that it may be inappropriate to assume linearity in the model, in terms of changes in logMAR, before patients have reached nadir. However, the company has stated that it would be impossible to include RHODOS in the integrated analysis as this would not allow linearity to be assumed. As described in the EAG report, the EAG considers that including RHODOS would not mean that linearity cannot be assumed, as transition probability up to 12 months could be derived using the propensity score weighting, with a regression approach used after 12 months, as in the company's base case. The EAG therefore considers that the company's reasoning for not including RHODOS in the integrated analysis due to assumptions around linearity is flawed.

2.4 Considerations Regarding Primary and Sensitivity Analysis

The EAG considers the company's points reflect a difference of opinion between the EAG and the company over their preferred approach. The EAG acknowledges that different assumptions can be used to analyse the current data. However, with regards to the choice of model, it is unclear to the EAG how well the MMRM and MI methods account for the large amount of missing data at each time point. The EAG notes that, although the estimated difference between idebenone and SoC arms is consistent across approaches, there are substantial differences between the MMRM and the MI methods for the estimated change from baseline of both the idebenone and SoC arms. In the company's preferred MMRM approach the effect of idebenone across all time points is more favourable compared to the results of MI models and statistically significant, whereas the results of the MI models are all statistically non-significant. Given these concerns, as well as the company's inability to demonstrate that missing data are missing at random (MAR), the EAG preferred the MNAR approach compared to the implicit MAR assumption implemented within the MMRM approach.

The EAG recognises the inherent limitations in the data that may not have allowed for visual acuity at nadir to be accounted for and appreciates that the company aimed to account for the prognostic factor of disease stage through the inclusion of time from onset and visual acuity at baseline. However, noting that baseline visual acuity may have been measured at any disease stage and the considerable variability between idebenone and SoC in the median and interquartile range of time from onset at baseline, the EAG is concerned that the stage of disease has not been adequately accounted for, as the aforementioned variability could indicate patients in each treatment group were at different disease stages at baseline.

2.5 Considerations Regarding Utilising Different Data Sources in the Economic Model

The EAG disagrees with the company's opinion that the best possible data sources have been used to ensure the clinical benefits of idebenone and SoC are captured in the model. As previously stated, the EAG considers that a more appropriate approach would have been to include RHODOS in the integrated analysis or, alternatively, use the PSW in the integrated analysis to match patients to the RHODOS patients. This would have avoided applying the RHODOS and integrated analysis treatment effects separately in naive succession and may have led to the model outcomes being better aligned with the RHODOS and the integrated analysis outcomes.

Error! Reference source not found. presents the changes in logMAR from baseline from RHODOS and the integrated analysis, compared to the company base case. While the company has stated in their letter that the model may not be fully aligned with clinical results at every time point from a single source, the EAG notes that for SoC patients, there is no close alignment with the clinical results at any time point.

Figure 1. Change in logMAR from baseline (model vs RHODOS & Integrated analysis outcomes)

2.6 Considerations Regarding Baseline Distribution of Patients

The EAG thanks the company for highlighting that adjusting the baseline population data in the model adjusts only the baseline characteristics of patients and not the baseline distribution of patients. The EAG notes that when assuming the RHODOS distribution of patients at baseline with the eight-state model, the RHODOS outcomes for SoC patients at six months (+0.127 change in

logMAR from baseline) are more closely replicated in the model (+0.122) compared to the company base case (+0.31).

As discussed in the EAG report, the EAG considers that as the RHODOS-derived treatment effects are applied in the model from baseline to six months, the distribution of patients at baseline should similarly be informed using RHODOS to more accurately reflect the trial outcomes in the model. Figure 2 presents the changes in logMAR when assuming the RHODOS distribution of patients at baseline, with RHODOS treatment effects applied up to six months and the integrated analysis treatment effects applied thereafter.

Figure 2. Change in logMAR from baseline (Integrated analysis vs RHODOS baseline distributions)

As shown in Figure 2, at six months the RHODOS trial outcomes for idebenone and SoC patients are accurately replicated in the model. After six months, treatment effects are informed using the integrated analysis treatment effects, with both SoC and idebenone patients following similar logMAR recovery trajectories, with logMAR improving compared to baseline by 36 months.

The EAG notes that when assuming the RHODOS distribution of patients in the model, the outcomes at 24-months closely align with the company's original PSM analysis, that compared idebenone patients from the LEROS ITT study to SoC patients from CaRS I & II. The PSM was previously conducted in response to EAG clarification question A2 at the first clarification stage. At 24 months in the model, change in logMAR for idebenone patients is -0.18 and -0.093 for SoC patients. In the company's original PSM analysis, change in logMAR for idebenone patients was measured at -0.13 and -0.11 for SoC patients. Table 1 provides the results of the company's original PSM analysis.

Table 1. PSM analysis of change in best VA at 24 months between idebenone treated patients (LEROS ITT) matched to SoC treated patients (CaRS-I and CaRS-II).

Treatment	Change in best VA at 24 months, logMAR LS-Means (95% CI)	LS-Means p-value
Idebenone	–0.13 (–0.27 to 0.02)	0.097
SoC	–0.11 (–0.26 to 0.04)	0.152
Difference	–0.02 (–0.23 to 0.19)	0.871

ANCOVA with treatment as covariate

Abbreviations: CI, Confidence interval; ITT, intention to treat; LS, least squares; logMAR, Logarithm of the minimum angle of resolution; PSM, propensity score matching; SoC, Standard of care; VA, Visual acuity

Source: Company response to clarification Table 8

The EAG also agrees with the company that the outcomes of the RHODOS trial are most accurately replicated in the model when assuming the eight-state model, with the four-state model overestimating the idebenone and SoC treatment effects up to six months. The EAG previously considered that the high number of health states combined with the limited number of patient observations was the primary driver of the difference between the model and RHODOS outcomes, with the four health state model providing changes in logMAR more aligned with RHODOS. The EAG now appreciates that the distribution of patients at baseline is the cause of the misalignment. As such, the EAG now agrees with the company that the eight-state model with the RHODOS distribution of patients at baseline accurately replicates the RHODOS outcomes in the model. Based on this, the EAG considers that the eight-state model is likely to be more appropriate than the four-state model, despite the small number of observations to inform the transition probabilities and the implications of the on-health state occupancy which the EAG's still considers to be a considerable source of uncertainty.

Therefore, in the absence of the ability to include RHODOS in the integrated analysis, the EAG considers that accurately replicating the RHODOS trial effects in the model and then applying the integrated analysis treatment effects is the most appropriate approach of the available options. As such, the EAG's preferred assumptions include using RHODOS to inform the baseline characteristics of patients and the distribution of patients at baseline in the eight-health state model. The EAG's updated deterministic and probabilistic base cases, with incremental and cumulative assumption outcomes, are presented in Section 3. As a scenario around the EAG base case, the EAG has also explored assuming the integrated analysis baseline patient distribution and characteristics with the EAG's preferred assumptions.

Finally, concerning the company's analysis which compares the integrated analysis outcomes to the model outcomes (Figure 3 in the company's letter). As the 12-month onward model outcomes have been taken in isolation, they fail to account for the RHODOS treatment effects applied from baseline to six months and the integrated analysis treatment effects from six to twelve months. Therefore, the model outcomes as presented in the company's analysis do not accurately reflect model outcomes in the company base case, as outlined in **Error! Reference source not found.**. With Figure 2 highlighting how logMAR can vary significantly when the integrated analysis treatment effects are applied, depending on which patient baseline logMAR has been used.

3 Scenario analysis and EAG base case

Table 2 presents the outcomes of the EAG's scenario analyses. Assuming the RHODOS distribution of patients at baseline is included in the updated list of EAG-preferred modelling assumptions (Table 3), with the eight-state model also being preferred. The EAG's updated deterministic and probabilistic base case results are provided in Table 4 with a scenario around the EAG base case using the integrated analysis baseline patient distributions and characteristics in Table 5.

Table 2. Results of the EAG's scenario analyses

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/ QALY)
Company base case	[redacted]	[redacted]	28,451
RHODOS distribution of patients at baseline	[redacted]	[redacted]	274,905

Abbreviations: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years.

Table 3. EAG preferred modelling assumptions

Preferred assumption	Independent ICER (£/QALY)	Cumulative ICER (£/QALY)
Company base case	28,451	-
RHODOS baseline characteristics of patients	28,864	28,864
RHODOS baseline distribution of patients	274,905	282,618
Transition probabilities up to 48 months	29,387	178,266
Integrated analysis – time to discontinuation	54,793	312,128
Lawrence *et al.* EQ-5D values[1]	40,666	431,467
No carer disutility	31,118	495,298
Meads *et al.* health care resource use[2]	29,299	496,888
Outpatient resource use applied to <1 logMAR health states	28,456	496,924
Supportive living applied as one-off cost	31,349	497,953
SoC patients require half idebenone outpatient visits	28,506	498,187

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Table 4. EAG base case results

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	498,187
Probabilistic results							
SoC	[redacted]	-	[redacted]	-	-	-	-
Idebenone	[redacted]	-	[redacted]	[redacted]	-	[redacted]	506,684

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

Table 5. Scenario around the EAG base case

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
EAG preferred modelling assumptions with the integrated analysis baseline patient distribution and characteristics							
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	92,002

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

EAG response to the company's letters, updated results.

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1 Introduction

The EAG (external assessment group) thanks the company for identifying a factual inaccuracy in how the RHODOS distribution of patients at baseline had been applied in the EAG's previous base case and scenarios. Provided in this report are the EAG's updated scenario and base case outcomes.

The EAG notes that while the identified inaccuracy leads to changes in the outcomes of the model, Figure 2 of the EAG's response to the company's letter, which presents the mean changes in logMAR from baseline when assuming the RHODOS distribution, remains factually accurate.

2 Updated Scenario analysis and EAG base case

Table 1 presents the updated outcomes of the EAG's scenario analyses, Table 2 the EAG's preferred modelling assumptions applied independently and cumulatively, Table 3 the EAG's deterministic and probabilistic base case results and Table 4 a scenario around the EAG's base case.

Table 1. Results of the EAG's scenario analyses

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case	[redacted]	[redacted]	28,451
RHODOS baseline characteristics and distribution of patients.	[redacted]	[redacted]	205,861

Abbreviations: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years.

Table 2. EAG preferred modelling assumptions

Preferred assumption	Independent ICER (£/QALY)	Cumulative ICER (£/QALY)
Company base case	28,451	-
RHODOS baseline characteristics of patients	28,864	28,864
RHODOS baseline distribution of patients	200,162	205,861
Transition probabilities up to 48 months	29,387	143,296
Integrated analysis – time to discontinuation	54,793	252,833
Lawrence *et al.* EQ-5D values[1]	40,666	326,865
No carer disutility	31,118	369,728
Meads *et al.* health care resource use[2]	29,299	372,158
Outpatient resource use applied to <1 logMAR health states	28,456	372,183
Supportive living applied as one-off cost	31,349	373,116
SoC patients require half idebenone outpatient visits	28,506	373,292

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Table 3. EAG base case results

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	373,292
Probabilistic results							
SoC	[redacted]	-	[redacted]	-	-	-	-
Idebenone	[redacted]	-	[redacted]	[redacted]	-	[redacted]	379,505

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

Table 4. Scenario around the EAG base case

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
EAG preferred modelling assumptions with the integrated analysis baseline patient distribution and characteristics							
SoC	[redacted]	[redacted]	[redacted]	-	-	-	-
Idebenone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	92,002

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