Part 1 – redacted

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

Chair presentation

Technology appraisal committee C [11 February 2025]

Chair: Richard Nicholas

Lead Team: Ugochi Nwulu, Rob Forsyth, Mark Corbett

Evidence review group: BMJ- TAG

Technical team: Harsimran Sarpal, Eleanor Donegan, Adam Brooke, Linda Landells, Ross Dent

Company: Chiesi

NICE

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

- ❑ ACM1 recap
- ✓ Draft guidance recommendations
- ✓ Issues from ACM1 and committee's conclusion
- ❑ ACM2
- ❑ Consultation response
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

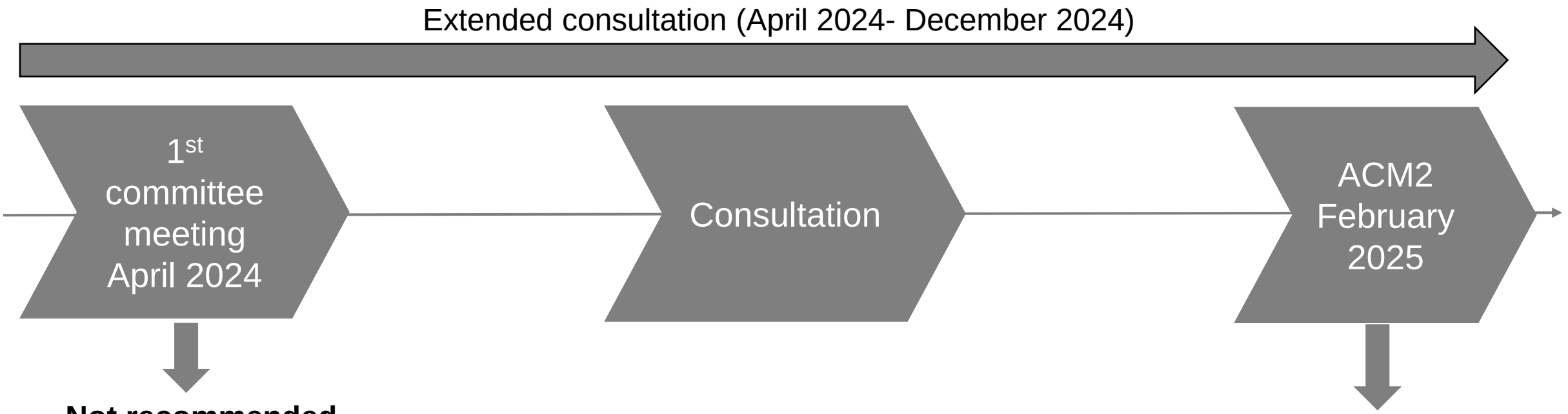
Committee decision making slide

	Question for committee
Long-term clinical and cost-effectiveness	• Does the company's integrated analyses (after 6 months) provide strong evidence of a clinically meaningful long-term treatment benefit of idebenone over SoC? • Should RHODOS be included in integrated analyses (EAG preference)? • Should RHODOS or integrated analysis baseline characteristics/distribution be used at the start of the model?
Health-related quality of life	• Which is the most appropriate source for deriving utilities HUI-3 or EQ-5D? • Is it appropriate to apply caregiver disutility for carers of adults?
Time on treatment	• Whose approach is more appropriate for time on treatment? • When should treatment with idebenone should be stopped?

NICE

Abbreviations: EQ-5D, EuroQol 5 Dimension; HUI, health utility index; SoC, standard of care

History of evaluation



Not recommended

- Uncertainties in ITC
- Insufficient evidence for 8 health states
- Uncertainties in modelling SoC treatment effect, time on treatment and utilities values

- Integrated analysis for treatment effectiveness and modelling
- Clinical validation for assumptions used in company's base case
- Updated PAS

Abbreviations: ITC, indirect treatment comparison; PAS, patient access scheme; SoC, standard of care

Draft guidance recommendations

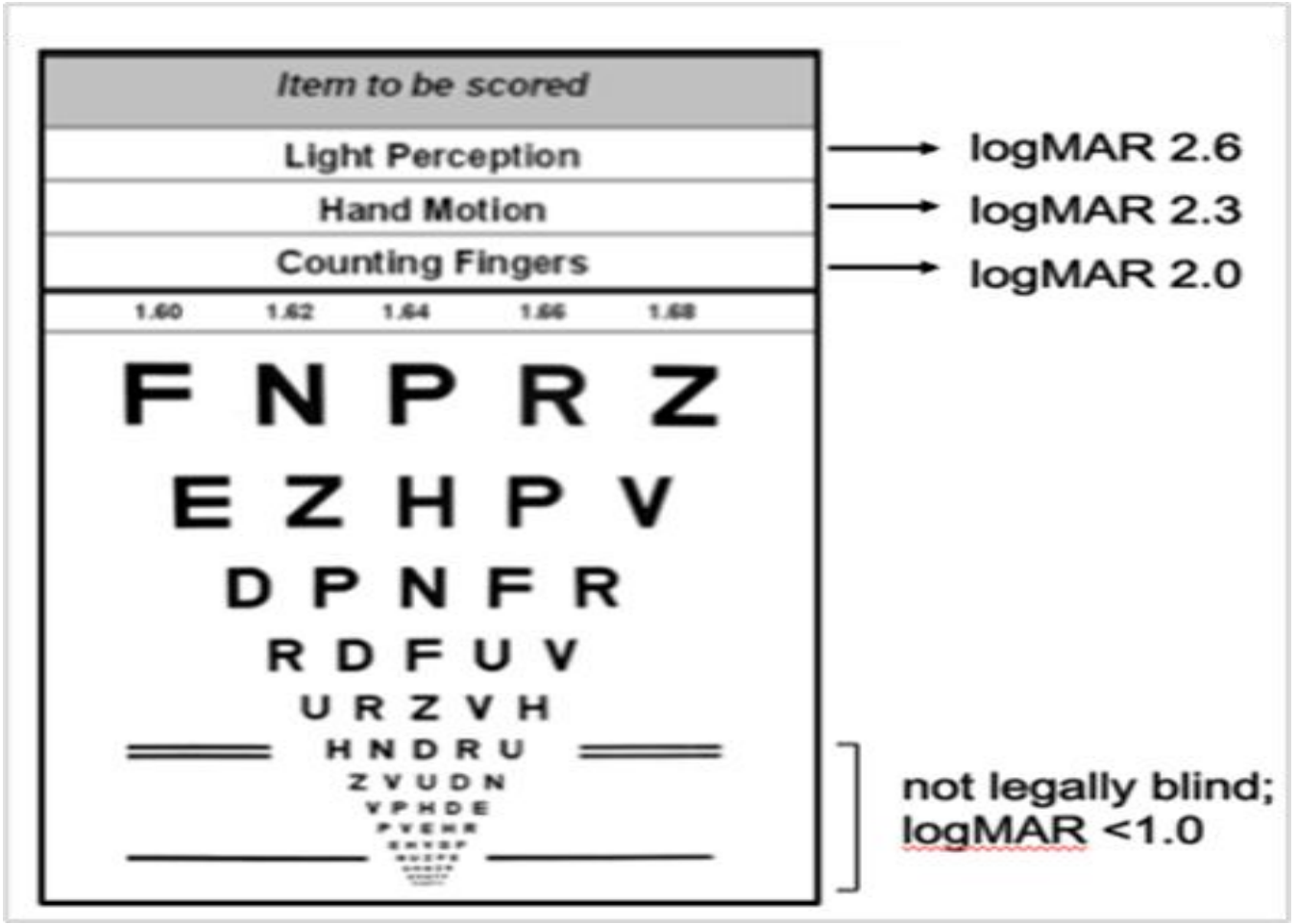
Direct RCT and ITC evidence suggested that idebenone was no better in improving vision than SoC
Due to clinical uncertainties in modelling a plausible ICER could not be determined

Idebenone is **not recommended** for treating visual impairment in Leber's hereditary optic neuropathy (LHON) in people 12 years and over

Abbreviations: LHON, Leber's hereditary optic neuropathy; SoC, standard of care

Main outcome Logarithm of minimum angle of resolution (logMAR)

- Vision loss in LHON is measured by logMAR in clinical trials
- Very rapid loss of VA with over 50% of eyes deteriorating to logMAR above 1.0 within one week of onset

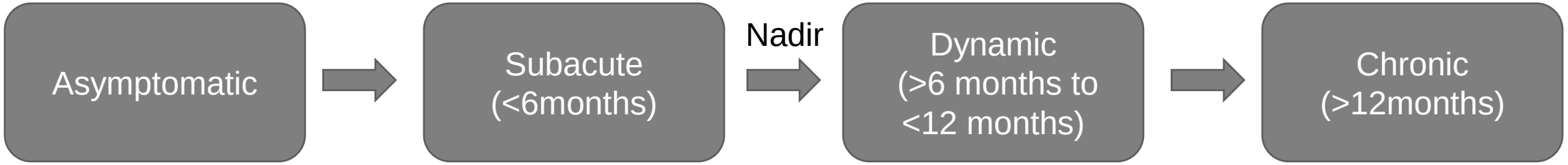


NICE

Abbreviations: LHON, Leber's hereditary optic neuropathy

Clinical course of LHON

VA in individual eye typically reaches its lowest point (nadir) in subacute phase



- Over 50% deteriorate to logMAR > 1 within one week of disease onset
- After 12 months, in dynamic phase more than 80% are classified as legally blind

Abbreviations: CI, confidence intervals; LHON, Leber's hereditary optic neuropathy; VA, visual acuity

Response to draft guidance consultation

- Company (Chiesi Ltd)
- - new integrated analysis using all clinical data
- - updated PAS
- LHON Society
- Web comments

NICE National Institute for Health and Care Excellence

Abbreviations: LHON, Leber’s hereditary optic neuropathy; PAS, patient access scheme

Consultation Responses – patients and LHON society

LHON Society

- Access to idebenone on the NHS in Wales/Scotland (for people with LHON who are not yet blind) but not England which is potentially discriminatory (in Equality Act 2010 covers England, Wales and Scotland)*
- LHON is a debilitating condition that leads to significant impacts on the person's life. There is a strong unmet need as idebenone is the only available treatment to people living in England
- EAG 4-health state model is inappropriate and shows a lack of understanding of the condition. Agree with the inclusion of separate off-chart health states (prefer company instead EAG's modelling approach- see slide)
- Carer disutility should have been applied - people agreed adults with LHON need daily supports

Web comments

- Idebenone could save a percentage of eyesight, meaning that they would not need support
- Generic idebenone is available on private prescription with suppliers in the USA or in Europe, lack of approval would lead to inequality based on both income and access to computers
- Access to idebenone would offset state NHS and PSS support for visual impairment/mental health issues

***NICE**: this is a misinterpretation of the Equality Act 2010. In addition, NICE and other HTA bodies and commissioners in Scotland and Wales have different and separate remits

Abbreviations: HTA: health technology assessment; LHON, Leber's hereditary optic neuropathy; PSS, Personal Social Services

Issues from ACM1 and committee's key conclusion

Key issues for committee discussion			EAG's view-resolved?
Clinical evidence	1	Non-randomised long-term evidence – uncertain magnitude of benefit ITC using propensity score matching was highly uncertain – insufficient population adjustment Should RHODOS be included in integrated analyses (EAG preference)?	Partially
CE section	2	Should RHODOS or integrated analysis baseline characteristics/distribution be used at the start of the model?	No
	3	Modelled time on treatment for idebenone - sensitivity analyses to be explored	No
	4	Uncertainties in utilities values that were not LHON and UK specific	No
	5	Inclusion of carer utility – prefer EAG's approach not including disutility for carers of adults	No

Abbreviations: ITC, indirect treatment comparison, LHON, Leber's hereditary optic neuropathy; SoC, standard of care

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

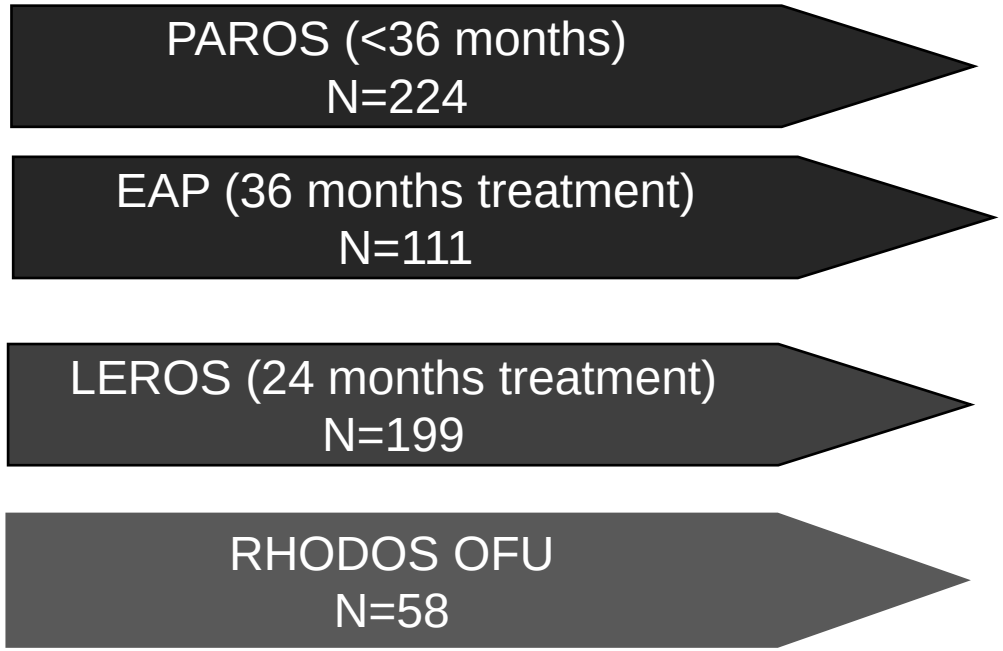
- ❑ **Key issues and background**
- ✓ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Updated integrated analysis

Draft guidance
- PSM doesn't provide reliable evidence of long-term benefit of idebenone compared with SoC
- Requested analyses using a more comprehensive view of entirety of the available evidence

Company
- Integrated analysis pooling evidence from RHODOS-OFU, EAP, LEROS and PAROS but excluded RHODOS (main trial)
- Including RHODOS would introduce bias
- Conducted propensity score weighting to address imbalance in prognostic factors between idebenone and SoC

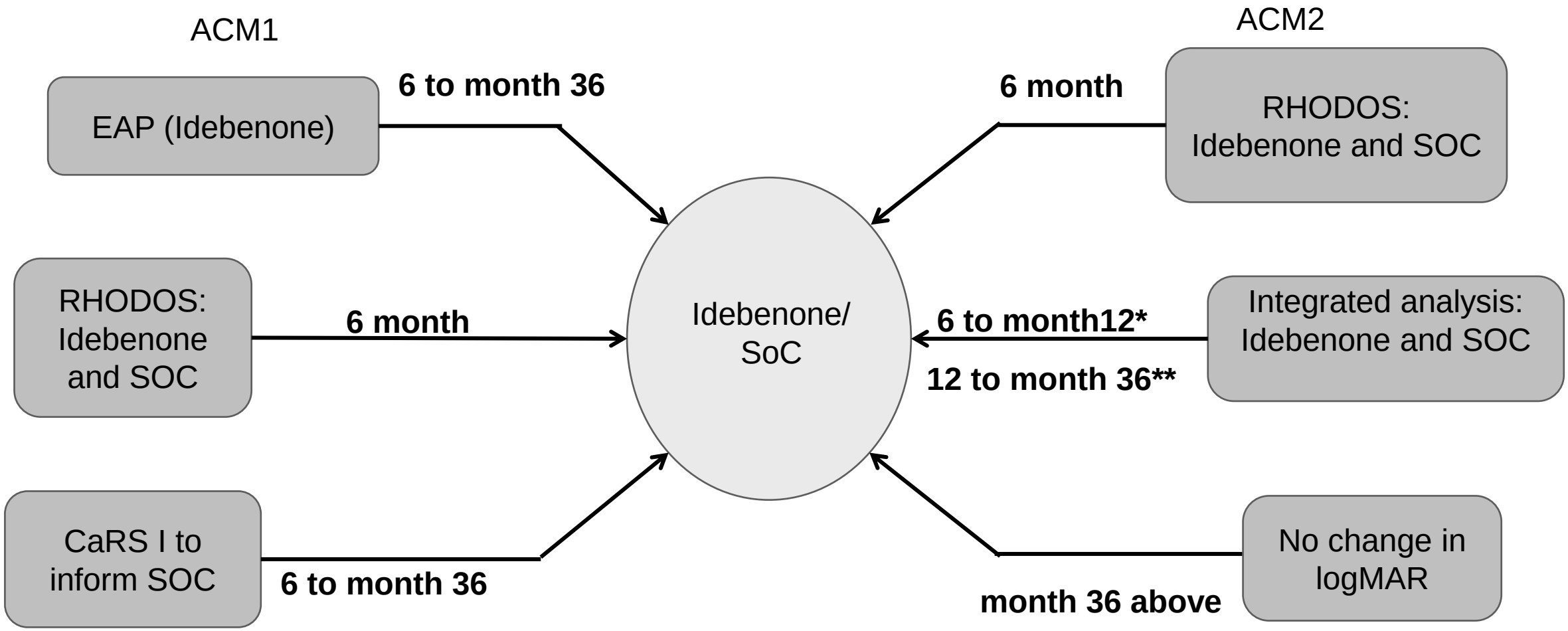


EAG
- Updated propensity score weighting potentially less biased than original approach
- PSWA aligned baseline characteristics of both treatment groups within integrated analysis but no consideration given to RHODOS baseline characteristics
  - RHODOS is used in model up to 6 months, then integrated analysis - may not be coherent

Abbreviations: EAP, expanded access program; LHON, Leber's hereditary optic neuropathy; OFU, observational follow-up; PSM, propensity score matching; PSWA, propensity score weighting analysis; SoC, standard of care

Should RHODOS be included in integration analysis?

Modelled treatment effect for idebenone and SoC



Abbreviations: CaRS, case record survey; EAP, Expanded Access Program; MAR, missing at random, MNAR, missing not at random PSW propensity score weighting; SoC, standard of care;

*Propensity score weights
**Logistic regression model with MAR and MNAR

Updated propensity score weighting analysis

Company

- Sex, age at onset, time from onset at baseline, BCVA, unilateral/bilateral involvement at baseline and type of mutation variable used in propensity score (PS) model
- Excluded people with missing data and VA at nadir from the analysis
- Clinical efficacy analyses performed using ITT population had at least one assessment on, or after, 12 months, excluding RHODOS

EAG

- Clinical experts: VA at nadir is an important prognostic factor not considered in regression analysis
- Although Idebenone and SoC groups are broadly aligned some differences in prognostic variables remain:
  - From 12 months, median time from 1st onset at baseline was 4.8 and 9.4 months in weighted SoC and idebenone treatment arms respectively
- Disease at baseline, a treatment effect modifier was not accounted for
- PSWA did not make populations similar to RHODOS and unable to compare with RHODOS

Does the PSWA using integrated analyses provide robust estimated for treatment effectiveness?

Abbreviations: BCVA, best-corrected visual acuity; ITT, intention to treat; SoC, standard of care; VA, visual acuity

Supplementary slide

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

- ❑ Key issues and background
- ❑ Clinical effectiveness
- ✓ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Large impact

Key issue: Model structure

At ACM1, company preferred 8 health state model, EAG preferred 4 health state model. Concerned

- whether enough data for 8 health states
- model did not replicate RHODOS outcomes

Company

- Highlighted inaccuracy that EAG applied RHODOS baseline characteristic but not distribution
- Applied baseline characteristics and distribution from integrated analysis in its base case

8 health state	4 health states
logMAR <0.3	Limited visual impairment
logMAR 0.3-0.6	Moderate visual impairment
logMAR 0.6-1.0	
logMAR 1.0-1.3	Visually impaired (on-chart)
logMAR 1.3-1.7	
Count fingers	Visually impaired (off-chart)
Hand motion	
Light perception	

EAG acknowledged inaccuracy, updated base case to use 8 health states

- Since RHODOS has been used to inform treatment effect from baseline, baseline should be informed using RHODOS and it means RHODOS trial outcomes are accurately reflected in the model (next slide, right panel)
- In contrast, using integrated analysis to inform baseline means SoC treatment effect considerably underestimated in the company model compared to RHODOS and the integrated analysis
  - Mean change in logMAR is at 6 months is [redacted](model) compared to [redacted](RHODOS), and [redacted](model) compared to [redacted](integrated analysis) at 36 months (next slide, left panel)
- Applied RHODOS baseline characteristics and distribution in its base case – this has a large impact on ICER

Should the RHODOS or integrated analysis baseline characteristics/ distribution be used at start of model?

Abbreviations: ICER, incremental cost-effectiveness ratio; SoC, standard of care;

Modelling treatment effect for idebenone and SoC

Figure: Change in logMAR from baseline (model vs RHODOS & Integrated analysis outcomes)

Figure: Change in logMAR from baseline (Integrated analysis vs RHODOS baseline distributions)

Is the SoC treatment effect accurately replicated in the model?
How should patients be distributed at baseline?

NICE

Abbreviations: SoC, standard of care

Large impact

Issue: Time on treatment

Figure: Time to indication discontinuation from integrated analysis

Figure: Time to discontinuation from integrated analysis

Company: ToT discontinuation using **indication** for stopping treatment obtained from integrated analysis:

- no clinically relevant benefit (CRR) in 24 months,
- 1st CRR is observed in 24 months, but no additional CRR observed in 6 months after 1st CRR
- 2nd CRR observed in 6 months after 1st CRR, no additional CRR observed in 6 months after 2nd CRR
- Company suggests formal stopping rule (next slide)

EAG:

- ToT calculated from integrated analysis data
- Time to discontinuation from integrated analysis more reflective of clinical practice as it represents when people actually discontinued treatment

Is using time to indication of treatment discontinuation from integrated analyses appropriate?

Abbreviations: CRR, clinically relevant benefit; ToT, time on treatment

Company's proposed idebenone stopping criteria

Company – stopping criteria based on CRR relative to the worst recorded VA (the nadir)

- "All patients will stay on treatment for a minimum of 24 months if there are no issues with tolerability
- Patients who have not experienced a CRR within 24 months will then stop treatment
- 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"

Is the company's proposed stopping criteria appropriate?
Does the company's modelling on previous slide reflect this ?

NICE

Abbreviations: CRR, clinically relevant recovery; VA, visual acuity

Issue: Health-related quality of life

Large impact

Health statethe	Company (HUI-3)	EAG (EQ-5D)
logMAR <0.3	0.84	0.79
logMAR 0.3 - 0.6	0.51	0.63
logMAR 0.6 - 1.0	0.44	0.57
logMAR 1.0 - 1.3	0.31	0.50
logMAR 1.3 - 1.7	0.29	0.50
Count fingers	0.17	0.37
Hand motion	0.15	0.35
Light perception	0.14	0.34

Company

- Used utility values from Lawrence et al based on HUI-3 instead of EQ-5D
- HUI-3 more appropriate as it includes questions specifically related to vision which captures the true burden in LHON
- Explored scenarios using utilities from Lawrence et al. 2023 (EQ-5D-5L and TTO), Brown et al, Czoski-Murray, and Rentz et al.

EAG

- EQ-5D is appropriate unless it is empirically demonstrated not to be the case for a given patient group. Lawrence et al. EQ-5D values are most appropriate for estimating the LHON utility; ensures uniformity across evaluations
- HST11: HUI-3 values lacked face validity and EQ-5D values more appropriate

Which utility values are more appropriate for decision-making?

Abbreviations: EQ-5D, EuroQol 5 Dimension; HM, hand motion; HUI, health state utility index; HST, highly specialised technology; LHON, Leber's hereditary optic neuropathy; TTO, time trade off

Large impact

Issue: Carer disutility

Draft guidance
- Excluding disutility values for carers of adults in all health states could be appropriate
- Could consider scenarios including a carer disutility for adults with LHON if more quantitative evidence for carers of adults with LHON or other conditions which causes blindness

Company
- Appropriate to use carer disutility for people with logMAR >1, to capture the real burden of LHON as the evidence of disutility of caregivers of people with LHON and other ophthalmology diseases is limited
- Caring for adults with LHON has significant negative impact on carer's quality of life
- Applied carer disutility from Wittenberg et al inline in HST 11 for people with logMAR >1

EAG
- HST11 only applied carer disutility for parents of children with a condition that causes blindness
- In LHON onset is early adulthood so inappropriate to apply a carer disutility for LHON
- Company has not provided quantitative evidence as requested by the committee
- Considered inappropriate to include carer disutility

Should disutility for carers of adults be applied in the model?

NICE

Abbreviations: HST, highly specialised technology; LHON, Leber's hereditary optic neuropathy; SE, standard error,

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

- ❑ Key issues and background
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Other considerations

Equality considerations

- Are there any equality issues that should be taken into account?

Uncaptured benefits

- Are there any benefits that have not been captured in the modelling?

Uncertainty

- Committee should be mindful that for rare diseases, evidence generation may be particularly difficult.
- In these specific circumstances, the committee may be able to make recommendations accepting a higher degree of uncertainty.
- Committee will consider how the nature of the condition affects the ability to generate high-quality evidence before applying greater flexibility

Summary of company and EAG base case assumptions

Assumption		Company preferred assumptions	EAG preferred assumptions
Clinical effectiveness		• RHODOS (baseline to six months) and integrated analysis	
Baseline	Characteristics	• Integrated analysis	• RHODOS
	Distribution		
Time on treatment		• Time to indication of treatment discontinuation based on clinical experts from Integrated analysis	• Integrated analysis
Utility values		• Lawrence et al HUI- 3	• Lawrence et al ED-5Q
Carer disutility		• Included	• Not included

*EAG was unable to make alternative assumptions for SoC treatment effect, so company's pessimistic treatment effect for SoC is assumed in EAG's base

Abbreviations: EQ-5D, EuroQol 5 Dimension; HUI, health utility index; SoC, standard of care

Cost-effectiveness results

- Company base case
- EAG base case and scenario analyses

Company base case results

Table: Deterministic results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	28,451
Idebenone	[redacted]	[redacted]			

Table: Probabilistic results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	29,311
Idebenone	[redacted]	[redacted]			

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

EAG's base case results

Table: Deterministic results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	373,292
Idebenone	[redacted]	[redacted]			
EAG preferred modelling assumptions with the integrated analysis baseline patient distribution and characteristics					
SoC	[redacted]	[redacted]	[redacted]	[redacted]	92,002
Idebenone	[redacted]	[redacted]			

Table: Probabilistic results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	379,505
Idebenone	[redacted]	[redacted]			

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

Impact of EAG preferred assumption on company base case

Table: Deterministic results

Scenario	Independent ICER £/QALY	Cumulative ICER £/ QALY
Company base		28,451
RHODOS baseline characteristics	28,864	28,864
RHODOS baseline distribution	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	40,666	326,865
No carer disutility	31,118	369,728
Meads et al. health care resource use	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: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care

Supplementary appendix

NICE National Institute for Health and Care Excellence

Idebenone (Raxone, Chiesi)

Table: Technology details

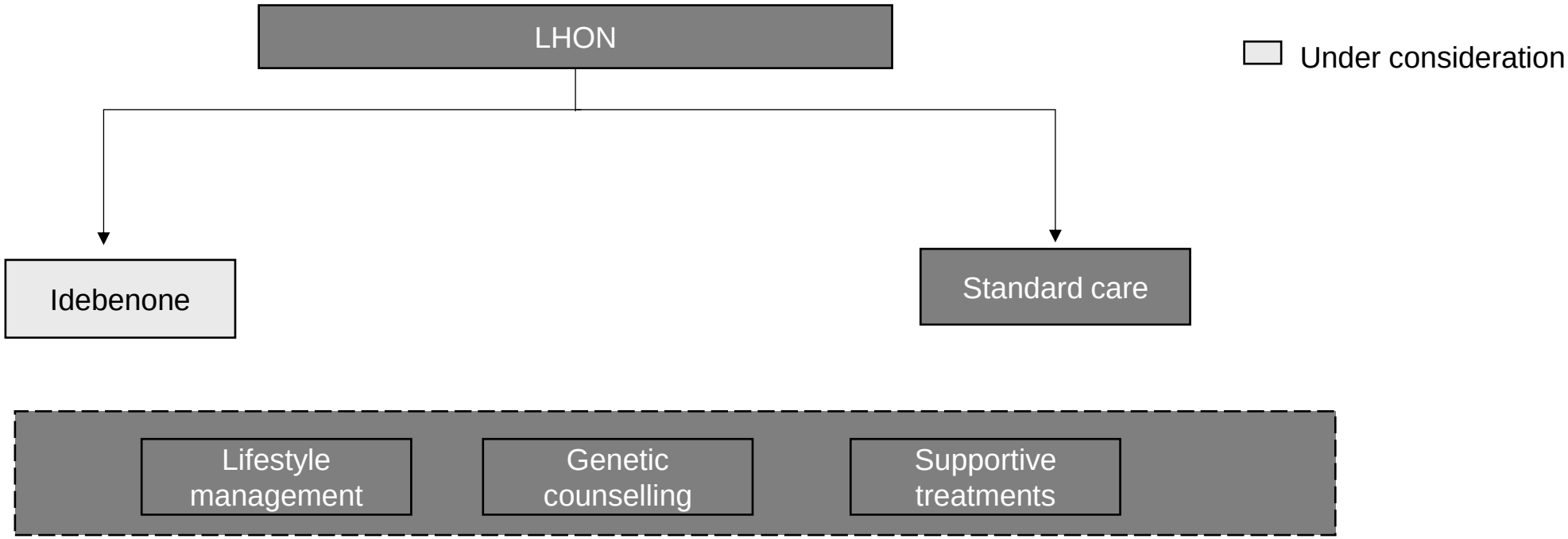
Marketing authorisation	'Idebenone is indicated for the treatment of visual impairment in adolescent and adult patients with LHON'
Mechanism of action	• Short-chain benzoquinone, is an antioxidant capable of transferring electrons directly to the mitochondrial electron transport chain • Reactivate viable-but-inactive RGCs in LHON patients by restoring cellular energy (ATP) generation
Administration	• Oral: 150 mg tablet • Licensed dose: 900 mg/day (2 tablets, three times a day)
Price	• List price: £6,364 for 180 tablets (30-day supply) • There is a proposed simple patient access scheme (PAS) discount for idebenone

Abbreviations: ATP, adenosine triphosphate; LHON, Leber's hereditary optic neuropathy; RGCs, retinal ganglion cells

Treatment pathway: no licensed treatments for LHON

Company: idebenone first and only treatment for LHON
EAG: large unmet need for people with LHON

- No UK treatment guidelines or approved treatment
- Company positioning idebenone as an alternative to best support care
- Clinical experts agreed treating an individual with confirmed LHON as soon as possible is desirable



Abbreviations : LHON – Leber's hereditary optic neuropathy

Key Studies: RHODOS, RHODOS-OFU, EAP and LEROS

EAG: Change in best VA considered most clinically relevant endpoint

	RHODOS (n=85)	RHODOS-OFU (n=58)	EAP (n=111)	LEROS (N=199)
Study design	Phase II, RCT (24 weeks treatment duration)	Observational follow (median 30 months) Single visit follow-up study	Open label retrospective non-controlled analysis of long-term VA (36 months)	Phase IV, open-label (24 month treatment)
Population	People aged ≥14 to <65 impaired VA in at least one eye LHON G11778A, T14484C, G3460A onset of visual loss is ≤ 5 years	People participated in RHODOS	Diagnosis of LHON onset of vision loss in second eye less than 12 months prior to the date of baseline visit	People ≥ 12 years Onset of symptoms ≤5 years of baseline LHON G11778A, T14484C, G3460A
Intervention	Idebenone	NA	Idebenone (named patient basis)	Idebenone
Comparator	Placebo	NA	No comparator	None
Outcomes	Changes / improvement in VA Contract sensitivity Retinal nerve fibre layer Visual field assessment HRQoL (VF-14 questionnaire)	VA: -change in best VA -change in VA both eyes -change in VA best eye	VA -CRR of VA from nadir -CRS of VA	CRR of VA from baseline

Abbreviations : CRR, Clinically Relevant Recovery; EAP, expanded access program; HRQOL, Health-related quality of life; LHON, Leber's hereditary optic neuropathy; OFU, observational follow-up; VA, visual acuity; VF, visual function;

EAG preferred scenario analyses

Table: Deterministic results

Scenario	Incremental		ICER £/ QALY
	Costs (£)	QALYs	
Company base case	[redacted]	[redacted]	28,451
Informing ToT using time to discontinuation from integrated analysis	[redacted]	[redacted]	54,793
Applying outpatient resource use to logMAR <1 health states using Meads et al.	[redacted]	[redacted]	28,456
RHODOS distribution of patients at baseline	[redacted]	[redacted]	205,861

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; ToT, time on treatment

Key Studies: Natural progression of LHON (CaRS I and CaRS II)

	CaRS-I (n=383)	CaRS-II (n=219)
Study design	Multicentre observation, retrospective, historical case record surveys • CaRS I informs SoC in economic model (mean follow [redacted])	
Population	Untreated people with genetically confirmed diagnosis of LHON, providing clinical data on the natural progression of LHON	
Inclusion/exclusion criteria	Inclusion criteria: • Genetically confirmed diagnosis • Data collected without pre-selection • No exclusion specified	Inclusion criteria: • Genetically confirmed diagnosis • Age≥12 years; • onset of symptoms was dated after 1999 and was well documented • At least two VA assessments were available within 5 years of onset of symptoms and prior to idebenone use • Genetic diagnosis for LHON for one of the following mtDNA mutations: m.11778G>A; m.3460G>A or m.14484T>C

NICE

Abbreviations: CaRS, case record survey; LHON – Leber's hereditary optic neuropathy; VA, visual acuity; SoC, standard of care

Baseline characteristics: Weighted vs. RHODOS

Variable		Integrated analysis		RHODOS	
		Idebenone	SoC	Idebenone	SoC
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

EAG

- Distribution of the 2 most prevalent mutations m.14484T>C and m.3460G>A differed to that of RHODOS
- Proportion of people in both arms matched but SDs differed considerably for the time from first onset at baseline ([redacted] vs [redacted]) for idebenone compared with SoC respectively

NICE

Abbreviations: NR, not reported, SoC, standard of care; SD, standard deviation

Multiple imputation method (12 month onwards)

EAG: prefers to assume data not missing at random (MNAR) to be least biased approach

Company

- To address missing data used 2 multiple imputation approaches:
  - MAR: assumed that data are missing at random
  - MNAR: assumed that data not missing at random
- Base case used logistic MAR from 12 months for idebenone and SoC - scenario using weighted MAR and logistic and weighted MNAR models

EAG

- MAR is a strong assumption; no sufficient justification was provided for preferring over MNAR
- MAR & MNAR reduce magnitude of idebenone treatment effect and increase uncertainty (standard error) compared with base case MMRM approach
  - MNAR is a less biased approach
- Available data substantially declines after month 24. Large loss of data & large imputed data over time may impact the robustness of the treatment effect estimates

Abbreviations: MAR, missing at random, MNAR, missing not at random; SoC, standard of care

Supplementary slide

Definitions: CRB and CRR

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

CRR was 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

NICE

Abbreviations : BCVA, Best-corrected visual acuity: CRB: clinically relevant benefit; CRR, clinically relevant recovery, CRS, clinically relevant stabilisation

Outcomes: integrated analysis (CRB)

Idebenone vs SoC	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48
Odds ratio	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio p-value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG

- At month 12, idebenone group had 3 times more likely to have CRB compared with SoC
- Substantially decline after month 24 in people with available data may have influenced robustness of effect estimates

Abbreviations: CRB, clinically relevant benefit; CI, confidence intervals; SoC, standard of care

Outcomes: integrated analysis (BCVA)

[redacted]

Company

- BCVA was analysed using MMRM, with an implicit imputation of missing values under MAR
- At month 12, slight improvement observed in idebenone logMAR ([redacted]) and worsening in SoC (approx. [redacted] letters on the ETDRS chart) ([redacted])
- At 18 to 24 months difference remained statistically significant for idebenone vs SoC

EAG

- Unclear if treatment effect of idebenone or SoC was consistent across 6-month intervals, (month 12-48), with variable visit timing (3-9 months) and missing observation data
- Substantially decline after month 24 in people with available data in idebenone arm may have influenced robustness of effect estimates

Abbreviations: BCVA, best-corrected visual acuity; ETDRS; Early Treatment Diabetic Retinopathy Study; MAR, missing at random,; MMRM, mixed model for repeated measures SoC, standard of care

Outcomes: integrated analysis (CRR)

[redacted]

Company

- Higher proportion of people met CRR criteria in idebenone group; supporting efficacy of idebenone
- idebenone group appeared to reach CRR significantly faster than the SoC group (p=[redacted])

EAG

- People in SoC achieved CRR without having treatment, suggesting spontaneous recovery
- CRR may be not a good indication of treatment effect and improved HRQoL
- Improvements in CRB and CRR may not differentiate between sight recovery and functional sight recovery

Abbreviations: CRB, clinically relevant benefit; CRR, clinically relevant recovery; HRQoL health related quality of life; SoC, standard of care

Issue: Health state resource use

Draft guidance

- Resource costs of outpatient visits (obtaining low-vision aids and rehabilitation) for health states with a logMAR< 1 was appropriate

Company

- Clinical validation highlighted that there is no longer a blind registration fee
- 1 clinician agreed that supportive living costs should occur over a lifetime horizon and not as a one-off cost as used by EAG. Company conducted 2 scenarios to address committee concerns:
  - Scenario 1: health care frequencies calculated using midpoint estimates b/w 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 company's clinical expert survey, and applying hospitalisation, depression and outpatient care costs for all health states

EAG

- Supportive living costs would likely involve a one-time assessment of the home environment rather than an ongoing assessment, so applied one-off cost with people having SoC with half the outpatient visits of idebenone in its base case
- Company's frequencies, informed by clinical experts, are substantially higher than Meads et al. which represents a much older population with more comorbidities

Abbreviations: SoC, standard of care

Supplementary slide

Small impact

Issue: Transition probabilities in PSA

Draft guidance

- Company's model lacks the functionality to allow idebenone and SoC transition probabilities to vary according to treatment effectiveness

Company

- Added functionality to allow idebenone and SoC transition probabilities in PSA
- Used SE values derived directly from base-case transition probabilities from the integrated analysis for 12 to month 36 in model
- Assumed SE of 0.11 in its base case calculated as the product of the transition probability and the transition variation parameter

EAG

- Some transition probabilities are only informed by a single observation, leading to unrealistic transitions that are guaranteed to occur which has high impact in model:
  - For SoC logMAR <0.3 people progressing to logMAR 1.3–1.7 health state in the 1st cycle of model
- SE for weighted and MNAR models depends on transition probabilities and variation, with higher patient transition leading to greater SE, 0.11 for 100% and 0.55 for 50%
- Consider treatment effectiveness uncertainties do not seem to be accurately captured in PSA, leading to an underestimation of treatment effect uncertainties in model

Abbreviations: MNAR, missing not at random; PSA, probabilistic sensitivity analyses; SE, standard error; SoC, standard of care

Health state resource use (scenario 1 & 2)

Table: Cost and resource use

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
Scenario 1 (midpoint estimates between the KOL survey and Meads *et al*)								
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%
Scenario 2 (applying resource use across all health states for hospitalisation and outpatient care costs only)								
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%
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; LHON, Leber hereditary optic neuropathy; LP, light perception

Main slide

NICE National Institute for Health and Care Excellence

Thank you.