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

Part 1– Confidential information redacted

Chair presentation

Technology appraisal committee C [8th July 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]

- ✓ ACM2 recap
- ❑ Consultation response
- ❑ Other considerations
- ❑ Summary

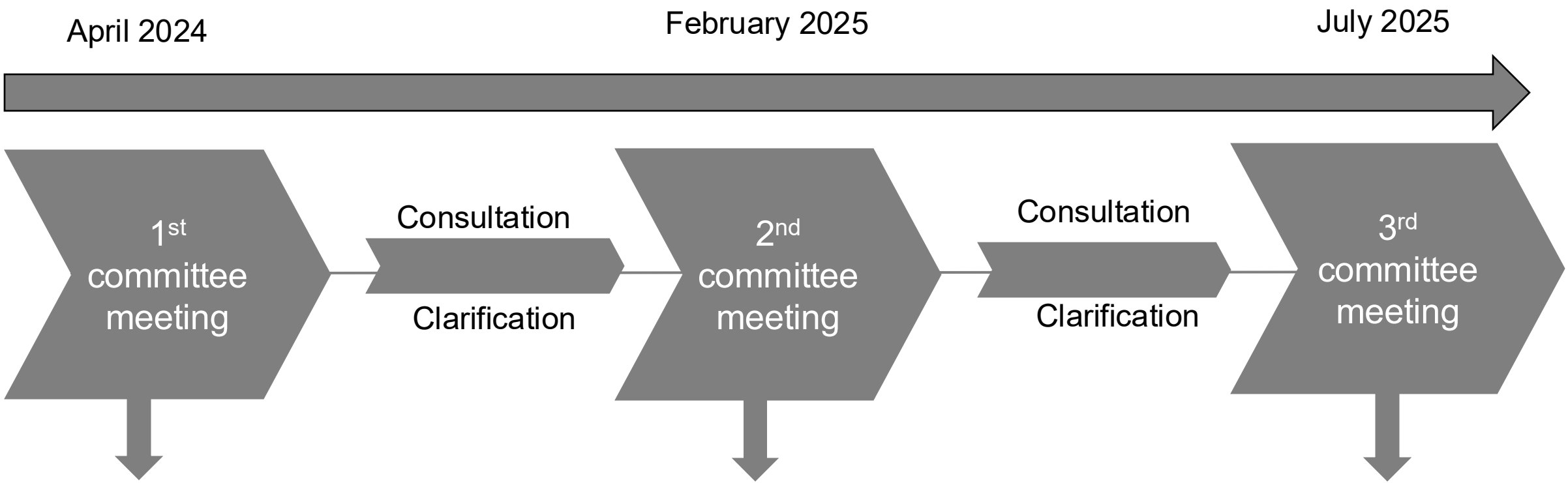
NICE National Institute for Health and Care Excellence

Draft guidance recommendations

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

History of evaluation



Uncertainties:

- Modelling SoC treatment effect, time on treatment and utility values

High level of uncertainty:

- Exclusion of RHODOS in PSWA, baseline distribution from IA
- Time on treatment & carer disutility

- Integrated analysis pooling all data
- Clinical validation
- Updated PAS

Abbreviations: IA, integrated analysis; PAS, patient access scheme; PSWA, propensity score weighting analysis; SoC, standard of care

Committee preferred assumptions at 2nd meeting & uncertainties

Assumption	Committee preferred assumptions
Baseline characteristics and distribution	Using RHODOS with 8-health state model
Time to treatment discontinuation	Time on treatment from the integrated analysis
Utility values	Consider HUI-3 from Lawrence et al. 2023 in decision making due to rarity of LHON
Disutility	No carer disutility for LHON adults

Uncertainties identified by the committee:

- exclusion of RHODOS from the company's PSWA
- using the baseline distribution from the integrated analysis instead of RHODOS
- when people would stop idebenone in clinical practice
- lack of quantifiable evidence on carer disutility

Abbreviations: LHON, Leber's hereditary optic neuropathy; HUI, health state utility index; PSWA, propensity score weighting analysis

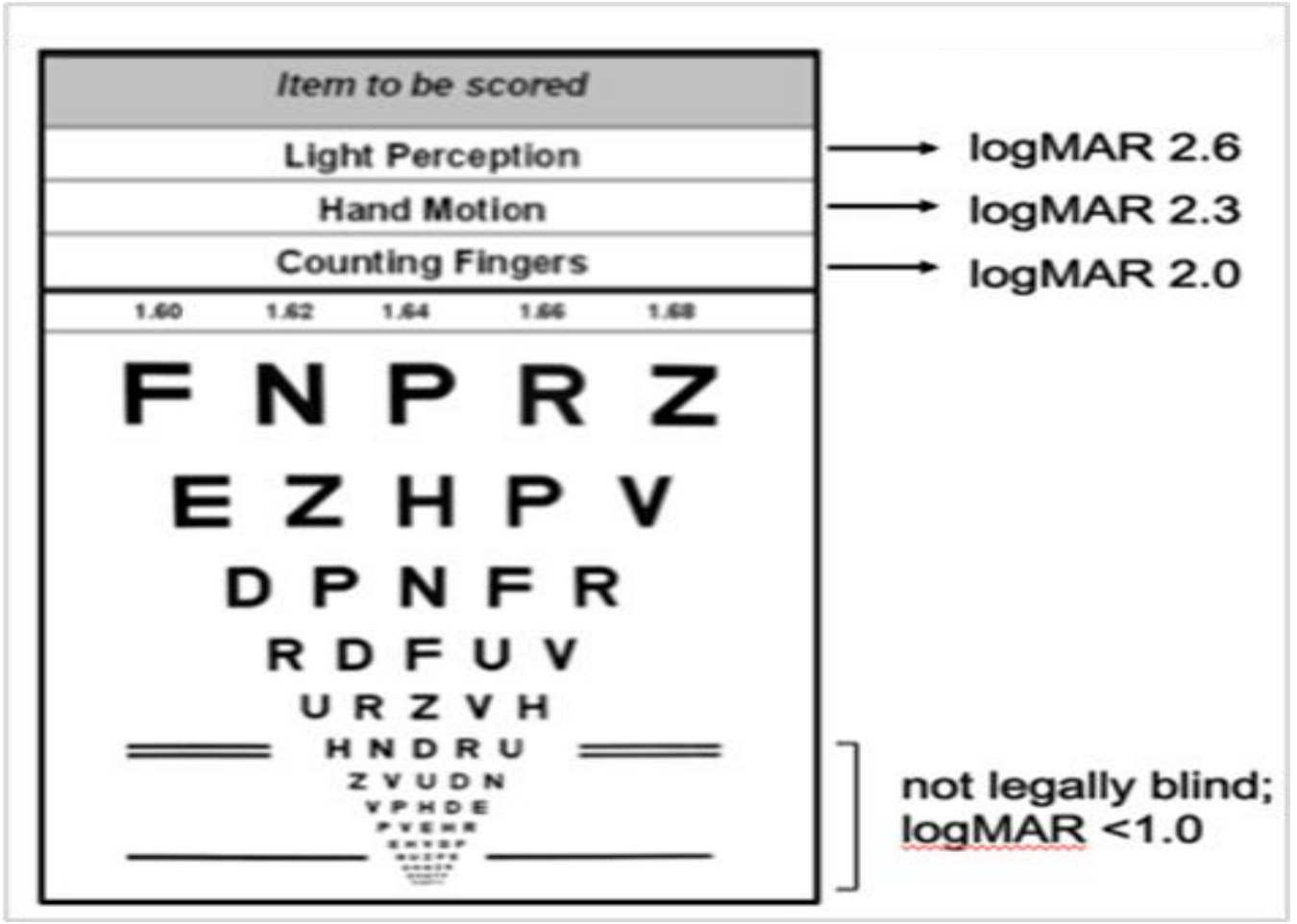
Key issues for committee discussion

Issue	Questions for committee
Source of efficacy data	• Is the company's integrated analysis of all trials or LEROS CaRS matched analysis (time since first symptom onset ≤1 year population) as preferred by the EAG more appropriate?
Time on treatment	• Is the company approach or EAG approach more appropriate for time on treatment? ○ EAG approach depends on source of efficacy data, but in both cases uses the time to treatment discontinuation data from the relevant data set
Health-related quality of life	• Which is the most appropriate source for deriving utilities HUI-3 or EQ-5D? • Is the company's or EAG's approach to apply carer disutility more appropriate?

Abbreviations: EQ-5D, EuroQol 5 Dimension; HUI, health utility index; PSWA, propensity score weighting analysis; 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

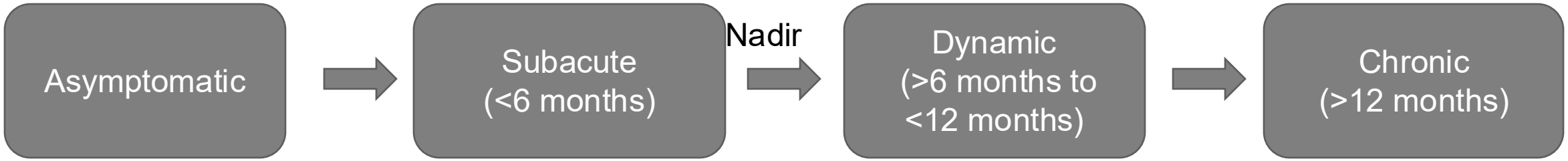


NICE

Abbreviations: LHON, Leber's hereditary optic neuropathy: VA, visual acuity

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

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

- ❑ ACM2 recap
- ✓ Consultation response
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Response to draft guidance consultation

- Company (Chiesi Ltd)
  - new integrated analysis using all clinical data
  - clinical validation
  - updated PAS
- LHON Society
  - conducted a survey
- Patient experts

NICE National Institute for Health and Care Excellence

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

Consultation responses – LHON Society & patient experts

LHON Society

- Appraisal seems to disregard many aspects of LHON that affect sight loss - relevant evidence on the impact of LHON on people with the condition and carers may not be fully considered
- Survey of qualitative and quantitative impacts of living with LHON patients and carers (n=38)
    - LHON significantly impacts QoL. People with the disease need significant support for daily tasks (guiding, reading, cooking, shopping, personal care, and transportation)
    - significant emotional, financial and social impact on caring for someone with LHON QoL of carers
    - see slide 19 for more information

Patient experts

- Evidence presented at committee meetings by clinical and patient experts appears to have been ignored in favour of the overly pessimistic view of the EAG
    - failure to understand the need for carers
    - late changes to EAG modelling before ACM2 – unclear on the validity of changes
- Evidence presented at the meeting was not considered, e.g. carer disutility

Abbreviations; LHON, Leber's hereditary optic neuropathy; QoL, quality of life

Updated integrated analysis

Draft guidance ACM 2

- "The committee would like to see impact of including the RHODOS data in the integrated analysis or use of PSWA to match the integrated analysis with RHODOS data"

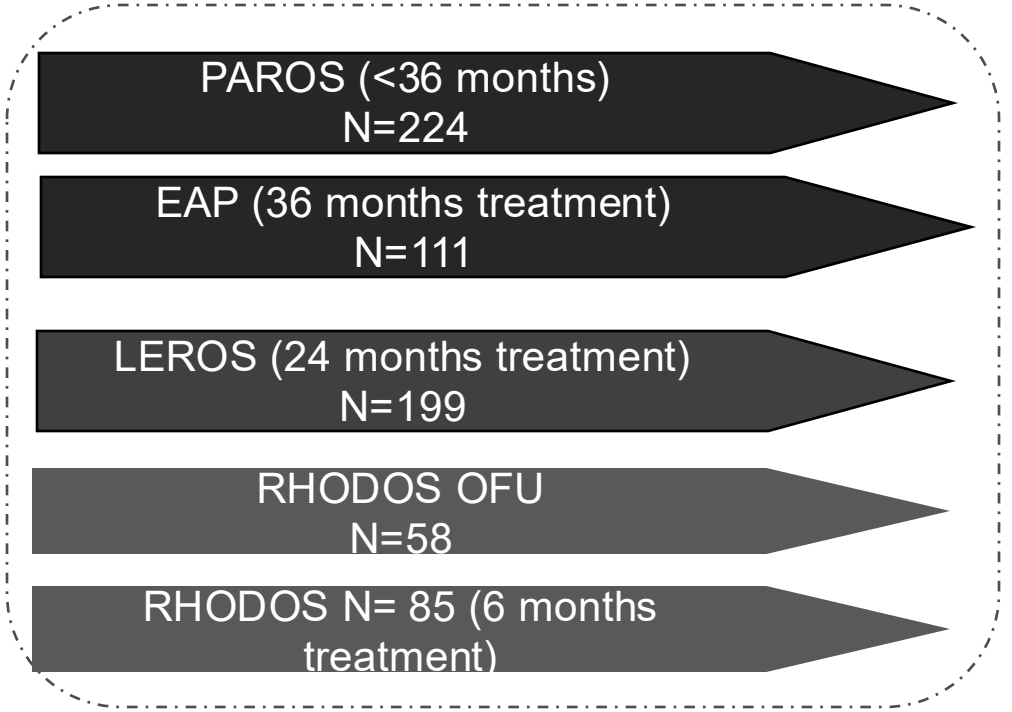
Company

- Submitted integrated analysis pooling evidence from RHODOS, RHODOS-OFU, EAP, LEROS, PAROS and CaRS I & II
- Propensity score weighting to address imbalance in prognostic factors between idebenone and SoC

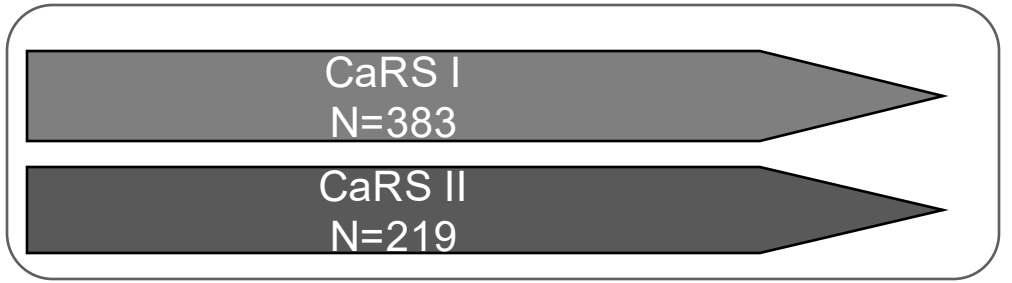
EAG

- Company did not analyse data up to 6 months using MMRM due to linearity assumptions being inappropriate before month 12
- No other alternative statistical methods explored which limits the comparability and robustness of integrated analysis results
- Unclear how RHODOS informs early treatment effect estimates

Idebenone studies



SoC LHON natural history studies



NICE

Abbreviations: EAP, expanded access program; OFU, observational follow-up; MMRM; mixed model for repeated measures PSM, propensity score matching; PSWA, propensity score weighting analysis; SoC, standard of care

Integrated analysis: missing data & baseline characteristics

EAG

- 29% of idebenone and 74% of SoC values are missing beyond month 12, requiring imputation methods using MAR and MNAR assumptions, consider missing data substantially increased the uncertainty
- Conclusions drawn from analyses beyond month 24 should be interpreted with caution

	Treatment	Month							
		6	12	18	24	30	36	42	48
Missing (%)	Idebenone	7%	29%	40%	49%	86%	87%	93%	91%
	SoC	40%	74%	86%	87%	92%	93%	93%	73%

EAG: weighted mean time since onset (key prognostic factor) was similar between treatment arms ([redacted] vs [redacted] months) but with large standard deviations and very different (weighted) medians ([redacted] vs [redacted] months) for idebenone and SoC respectively

- Indicates means are heavily skewed by outliers, and mean-based weighting may not be appropriate

Variable	Integrated analysis		RHODOS (ITT)	
	Idebenone	SoC	Idebenone	SoC
Analysis age (at first onset), mean	[redacted]	[redacted]	NR	NR
Time from first on set at baseline (months), mean (SD)	[redacted]	[redacted]	22.8 (16.2)	23.7 (16.4)
Baseline best visual improvement (logMar), mean (SD)	[redacted]	[redacted]	1.61 (0.64)	1.57 (0.61)

Abbreviations: ITT, intent to treat; MAR, missing at random, MNAR, missing not at random ;NR, not reported, SoC, standard of care; SD, standard deviation

Supplementary slide

Issue 1: Source of efficacy data

EAG

- Integrated analysis included trials of both incident and prevalent populations
  - time since first onset of symptoms ranged from [redacted] months for idebenone and [redacted] for SoC
- Integrated analysis mostly reflects prevalent rather than incident (newly diagnosed) population, but incident population is more likely to have idebenone in the NHS
  - stratifying integrated analysis by time since onset may have been more appropriate
- In absence of integrated analysis stratified by time since onset, company's previously presented LEROS CaRS matched analysis, stratifying by time since onset (≤1 year vs >1 year), may be more appropriate
  - CaRS contributed 93% of SoC patients in the integrated analysis (100% after 6 months), while LEROS contributed the largest proportion of idebenone patients (51% at baseline, increasing after six months as RHODOS patients are no longer followed up) → significant overlap between data sets
  - Results of the integrated analysis more closely resemble LEROS time since onset ≤1 year population, which is indicative of incident population, so consider LEROS CaRS matched analysis for population with time since symptom onset ≤1 year more appropriate for decision making (see slide)

NICE

Is integrated analysis or LEROS CaRS matched analysis using time since symptom onset ≤1 year more appropriate?

Abbreviations: IA, integrated analysis; PSWA, propensity score weighting analysis; SoC, standard of care

Issue 2: Time on treatment

Large impact

Time to indication discontinuation from integrated analysis

Time to discontinuation from integrated analysis

Company:

- Time on treatment using indication for stopping treatment obtained from integrated analysis and expert opinion on stopping treatment
- Model allowed people to continue treatment if they show continuing improvement in visual acuity beyond 36 months

EAG: acknowledge that the probable time to indication discontinuation more accurately reflects future clinical practice

- Company model did not consider the link between idebenone time on treatment and treatment benefits
- Time on treatment from integrated analysis, most appropriate but contradicts clinical expert opinion
- Presented 2 scenarios: 1) all people discontinue after 5 years; 2) all censored people assumed to have stopped treatment

Issue 2: Time on treatment

Idebenone treatment discontinuation, integrated analysis and scenarios

Integrated analysis and LEROS time to discontinuation comparison

EAG

- Scenario 1 (5 years) most conservative as costs are accounted for all people who receive benefit overtime
- Scenario 2 (integrated analysis censoring): censored people may continue treatment and incur costs, accounting for the treatment benefits without the treatment costs
- **If LEROS CaRS matched analysis data used for efficacy (EAG preference), the relevant time to treatment discontinuation data more closely reflects expected clinical practice (right panel above)**

NICE

Which is the most appropriate to estimate ToT?

Abbreviations: ToT: time on treatment, TTD, time to treatment discontinuation

Large impact

Issue 3: Health-related quality of life

Company ACM2
- Used utility values from Lawrence et al. based on HUI-3 and consider these more appropriate than EQ-5D

Draft guidance (DG2)
- "The committee recognised the difficulties in the ability to collect or generate clinical evidence in a rare condition and determined that it would consider HUI-3 utility values in its decision making"

EAG
- Disagreed with the company's opinion that there is poor convergence between Lawrences et al. EQ-5D values and visual decline
- Consider EQ-5D values to be more appropriate - they show a decline with visual deterioration and are also comparable to utility values identified in previous TAs (see slide)
- HUI-3 utilities most pessimistic; shows steep decline between health states and lowest utility for off-chart health states, which are equivalent to people with end-stage terminal cancer (e.g. Pourrahmat et al. 2021)

Abbreviations: EQ-5D, EuroQol 5 Dimension; HUI, health state utility index; LHON, Leber's hereditary optic neuropathy; TA, technology appraisal

Issue 3 : Health-related quality of life

Large impact

-0.33 decrement

Health state	Brown et al.1999 (TA283)	Lawrence et al. EQ-5D-5L	Lawrence et al. HUI-3	Lawrence et al. TTO	Czoski-Murray (TA298)	Rentz et al. (HST 11)
logMAR <0.3	0.84	0.79	0.84	0.88	0.71	0.92
logMAR 0.3 - 0.6	0.77	0.63	0.51	0.76	0.68	0.85
logMAR 0.6 - 1.0	0.67	0.57	0.44	0.70	0.51	0.80
logMAR 1.0 - 1.3	0.63	0.50	0.35	0.57	0.51	0.72
logMAR 1.3 - 1.7	0.54	0.50	0.33	0.53	0.31	0.69
Count fingers	0.52	0.37	0.21	0.41	0.31	0.53
Hand motion	0.35	0.35	0.19	0.43	0.31	0.38
Light perception	0.35	0.34	0.18	0.36	0.31	0.26

Off-chart utilities similar to end-stage cancer

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; TA, technology appraisal TTO, time trade off

LHON Society survey

Participants: 38

- 50% with LHON
- 50% Caregiver

"LHON impacts on all aspects of my daily life. I cannot do daily life normal tasks without some level of assistance e.g. shopping, cooking or studying"

Key highlights

- ✓ LHON impacts all aspects of life (independence, social and financial)
- ✓ People need significant support for daily tasks
- ✓ Carers feel emotional, practical, financial, and social impacts, which cause them stress, anxiety and depression
- ✓ Average of 1.58 carers, on average of 24.8 days out of 31 per month (average of 1.3 carers over the month)

"My husband is afflicted which means that I am his full-time carer and have to drive him everywhere."

"It impacts everything I do. I am often lonely and reliant on others."

NICE National Institute for Health and Care Excellence

Abbreviations: LHON, Leber's hereditary optic neuropathy

Carer disutility

ACM2 Company included disutility for carers of people with LHON with logMAR > 1
DG2 "Carer disutility not included… committee would like to see the amount of assistance and impact on carer's quality of life quantified, including the number of carers per person and the impact of treatment on carer HRQoL"

Company
- Appropriate to use carer disutility for people with logMAR >1 not living in residential care
- LHON Society survey suggest caring has a severe impact on 50% of people, moderate impact on 36% of people, and 75% of people experience anxiety
- Applied 0.04 disutility, and 1.3 continuous carers required in model

EAG
- Agreed with including carer disutility in model based on LHON society survey
- But considered company's approach to apply carer disutility on a per carer basis inappropriate
  - applied 0.04 disutility as an absolute value because caring is shared between carers
- Change has a minor impact on the cost-effectiveness results

Is the company's or EAG's approach to applying carer disutility more appropriate?

Abbreviations: LHON, Leber's hereditary optic neuropathy; HRQoL, health-related quality of life

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

- ❑ ACM2 recap
- ❑ Consultation response
- ✓ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Other considerations

Equality considerations

- No new equality issues raised
- 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 - if using integrated analysis	EAG preferred assumptions – if using LEROS CaRS matched analysis
Treatment effect	• Integrated analysis	• Integrated analysis	• LEROS CaRS matched analysis (time since first symptom onset ≤1 year)*
Time on treatment	• Time to indication of treatment discontinuation from integrated analysis	• Integrated analysis time to treatment discontinuation	• LEROS time to treatment discontinuation
Utility values	• Lawrence et al. HUI-3	• Lawrence et al. ED-5Q	• Lawrence et al. ED-5Q
Carer disutility	• Applied 0.04 disutility, and 1.3 carers	• Applied 0.04 disutility as an absolute value	• Applied 0.04 disutility as an absolute value

*In absence of stratified integrated analyses EAG provided scenario using LEROS CaRS matched analysis. Scenario required EAG to make assumptions about how patients are distributed between health states.

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]	28,241
Idebenone	[redacted]	[redacted]			

Table: Probabilistic results

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

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

EAG base case results

Table: Deterministic results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Using integrated analysis					
SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Idebenone	[redacted]	[redacted]			78,609
LEROS CaRS matched analysis: time since first symptom onset ≤1 year & LEROS TTD					
SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Idebenone	[redacted]	[redacted]			68,471

Table: Probabilistic results – using integrated analysis

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Idebenone	[redacted]	[redacted]			79,393

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

EAG's alternative base case results

Table: Deterministic results

	Scenario	Incremental		ICER £/QALY
		Costs(£)	QALY	
	Company base	[redacted]	[redacted]	28,241
1	LEROS CaRS matched analysis **+ HUI-3 utility values**	[redacted]	[redacted]	46,349
2	Integrated analysis treatment effects **+ all people discontinue treatment after five years**	[redacted]	[redacted]	61,903
3	Integrated analysis treatment effects **+ all censored people assumed to have discontinued treatment**	[redacted]	[redacted]	49,033

Abbreviations: HUI, health utility index; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care; TTD, time to discontinuation

Key issues for committee discussion

Issue	Questions for committee
Source of efficacy data	• Is the company's integrated analysis of all trials or LEROS CaRS matched analysis (time since first symptom onset ≤1 year population) as preferred by the EAG more appropriate?
Time on treatment	• Is the company approach or EAG approach more appropriate for time on treatment? - EAG approach depends on source of efficacy data, but in both cases uses the time to treatment discontinuation data from the relevant data set
Health-related quality of life	• Which is the most appropriate source for deriving utilities HUI-3 or EQ-5D? • Is the company's or EAG's approach to apply carer disutility more appropriate?

NICE

Abbreviations: EQ-5D, EuroQol 5 Dimension; HUI, health utility index; PSWA, propensity score weighting analysis; SoC, standard of care

Supplementary appendix

NICE National Institute for Health and Care Excellence

Patient perspectives

Living with LHON

- Diagnosis came as a shock, felt heartbroken and had to adjust to vision loss very quickly

Unmet need

- No treatments available and have to buy privately from the US or Poland
- People living in England have no access to treatment. But prescribed in Wales, Scotland, and Northern Ireland

Idebenone

- Idebenone has saved my sight, and has no disadvantage as it has stopped my manifestation and spreading
- Having idebenone early will improve quality of life, and without it, there could be serious visual impairment
- Idebenone should not be a postcode lottery (some NHS trusts help others, but others are overlooked as they are not aware of the disease)

Abbreviations: LHON, Leber's hereditary optic neuropathy

Time from first onset at baseline

NICE

Abbreviations: Bsl, baseline; SoC, standard of care

Issue 1: Integrated analysis vs. LEROS CaRS matched analysis

	Mean logMAR		Change from baseline		Difference
	Idebenone	SoC	Idebenone	SoC	
Integrated analysis					
Baseline	[redacted]	[redacted]	-	-	-
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LEROS CaRS matched analysis: first symptom onset ≤ 1 year					
Baseline	[redacted]	[redacted]	-	-	-
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LEROS CaRS matched analysis: first symptom onset > 1 year					
Baseline	[redacted]	[redacted]	-	-	-
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SoC, standard of care

Idebenone (Raxone, Chiesi)

Table: Technology details

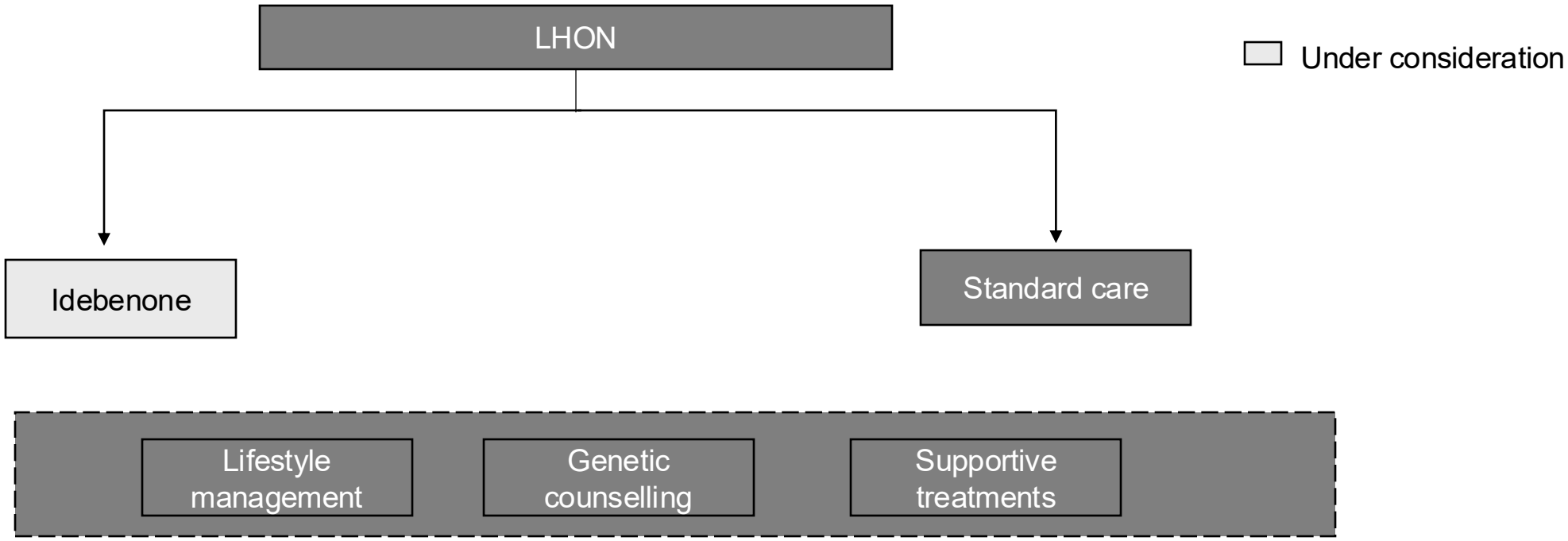
Marketing authorisation	'Idebenone is indicated for the treatment of visual impairment in adolescent and adult patients with LHON'
Mechanism of action	• Short-chain benzoquinone, is an antioxidant capable of transferring electrons directly to the mitochondrial electron transport chain • Reactivate viable-but-inactive RGCs in LHON 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



NICE

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; CRS, clinically relevant stabilisation; 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;

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

Multiple imputation method (12 month onwards)

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

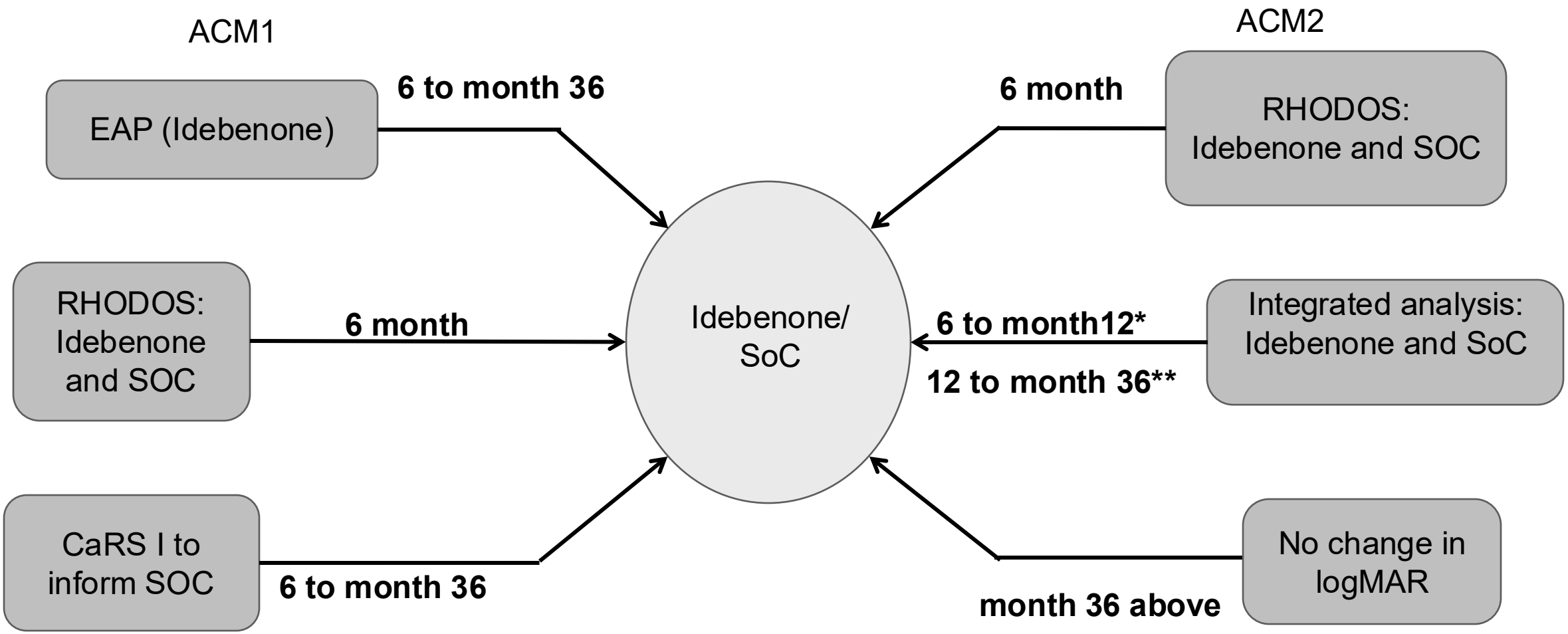
EAG

- 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

NICE

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

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

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"

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

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

NICE National Institute for Health and Care Excellence

Thank you.