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Clinical evidence review of idebenone for treating visual impairment in adults and young people with Leber's hereditary optic neuropathy

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About this clinical evidence review

Clinical evidence reviews are a summary of the best available evidence for a single technology within a licensed indication, for commissioning by NHS England. The clinical evidence review supports NHS England in producing clinical policies but is **not NICE guidance or advice**.

Summary

This evidence review considers idebenone for treating visual impairment in people with Leber's hereditary optic neuropathy (LHON).

A literature search identified 2 published studies (Klopstock et al. 2011 and Rudolph et al. 2013) appropriate for inclusion in the review. Additional evidence was taken from evidence described in the European public assessment report (EPAR, including data from an expanded access programme (EAP), RHODOS-OFU and a case record survey).

The primary effectiveness evidence comes from a phase II multicentre, double blind placebo controlled randomised controlled trial (RCT; RHODOS, Klopstock et al. 2011; n=85; idebenone n=55; placebo n=30), which included people aged between 14 and 64 years of age experiencing vision loss due to LHON within the previous 5 years, and having 1 of the 3 main mutations associated with LHON. Additional evidence came from a post-hoc analysis of a sub-population completing the main RHODOS study (Rudolph et al. 2013). The EPAR also reports on a longer-term open-label follow-up of patients who took part in RHODOS (the RHODOS-OFU), an analysis of an open label uncontrolled study, where eligible patients were prescribed idebenone in an expanded access programme (EAP) and a summary of a case-record survey of people with LHON (with and without receiving idebenone).

Effectiveness

The primary outcome in RHODOS, best recovery/least worsening of visual acuity in either right or left eye from baseline to 24 weeks, resulted in a mean improvement of 6 letters in people receiving idebenone compared with a 3 letter improvement in people receiving placebo (a 3 letter difference between groups, on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, however this was not statistically significant, logMAR = -0.064, 95% CI: -0.184 to 0.055, p=0.291).

Further analyses of RHODOS showed that among the patients with discordant VA at baseline (a difference of logMAR >0.2 between eyes) a statistically significant difference between treatment groups was found for all primary and secondary outcomes (best recovery/ least worsening logMAR = -0.285; 95% CI: -0.502 to -0.068; p = 0.01); best visual acuity (logMAR = -0.421; 95% CI: -0.692 to -0.150; p = 0.003;); change in visual acuity of the patient's best eye (logMAR = -0.415; 95% CI: -0.686 to -0.144; p = 0.003), and for all eyes (logMAR= -0.348; 95% CI: -0.519 to -0.176; p = 0.0001), suggesting there may be a beneficial effect for idebenone for

people with discordant visual acuities between the two eyes. Results from a responder analysis of people completing the RHODOS trial (reported only in the EPAR) who achieved a clinically relevant recovery (CRR i.e. improvement of at least logMAR 0.2 for patients with “on-chart” VA at baseline, or an improvement from “off-chart” to at least logMAR 1.6 for patients with “off-chart” VA at baseline), found 18 people (34%) receiving idebenone compared with 3 people (10.7%) receiving placebo, achieved a CRR from their lowest reported VA, in favour of idebenone (p=0.0321). Additional findings of observational data taken from an expanded access programme (EAP) and on data showing the natural course of vision loss and recovery in patients with a genetically confirmed diagnosis of LHON, supported these findings.

Results from a single observational follow-up visit (RHODOS-OFU) in people originally completing RHODOS but where the majority did not receive further idebenone treatment showed there was no difference between groups from RHODOS *end-point* to the time of their follow-up (a mean time of 2.5 years). The EPAR stated that “the in-between group difference was maintained, suggesting that the benefit obtained with idebenone after 6 months treatment persisted even after withdrawal of treatment”. People who originally received idebenone experienced an improvement of 6 letters, compared with a mean worsening of 1 letter for the placebo group, from original RHODOS *baseline* to the time of the follow-up visit (a mean time of 36 months), but this was not significantly different (p=0.0845).

A secondary outcome of RHODOS and the main analysis of Rudolph et al. (2013) was to assess changes in colour-contrast vision and considered any colour-contrast sensitivity of protan (red-green) and tritan (blue-yellow) colour vision. A sub-population of 39 patients at 1 site participating in RHODOS were assessed and the difference between treatment groups was presented as a percentage change, where a negative value showed an improvement in of colour vision. That analysis found a statistically significant improvement between treatment groups for tritan colour contrast at both 12 weeks follow-up (difference between groups: -14.51%; 95% CI: -24.19 to -4.83; p = 0.004) and 24 weeks follow-up (difference between groups: -13.63%; 95% CI: -23.61 to -3.66; p = 0.008). The changes in protan colour contrast were not statistically significant at 24-week follow-up (difference between groups = -

3.9%, p=0.239). The post-hoc analysis by Rudolph et al. (2013) sought to explore the inconsistencies in the results and found people with a discordant VA between eyes at baseline (a difference of logMAR ≥0.2 corresponding to 2 lines on the ETDRS chart) taking placebo showed a statistically significantly larger decline in protan colour contrast sensitivity when compared with idebenone, resulting in a statistically significant difference between groups at both 12 and 24-weeks follow-up. When the data was further analysed by age of patient, the results found the difference between treatment groups showed a statistically significant improvement in tritan colour contrast sensitivity for people who were younger than 30 years at baseline at both 12 and 24 weeks.

Health-related quality of life, measuring the patients self-reported interpretation of the impact of visual impairment on their functional activities as assessed using the Visual Function-14 (VF-14) validated scale. The Clinician's Global Impression of Change (CGIC) was a clinician reported interpretation of the change in patient's illness severity and this was also assessed.

These outcomes were included in RHODOS which found at 24 weeks follow-up, there was no difference in the change of scores between people receiving idebenone or people receiving placebo (estimated mean treatment difference = -1.37; 95% CI = -6.25 to 3.51; p=0.577). Similar findings were reported in the RHODOS-OFU, which found the changes recorded during RHODOS and RHODOS-OFU were small and the differences between idebenone and placebo groups were not statistically significant.

Safety and tolerability

In RHODOS the treatment drug was well tolerated with most adverse events being mild or moderate in intensity and included headache and nasopharyngitis as the most commonly reported. The two serious adverse events reported (1 in the idebenone treatment group and 1 in the placebo group) were considered unrelated to the treatment medication. No deaths were reported in RHODOS. Similar findings were found in the EAP, with most adverse events regarded as mild or moderate. The reported serious adverse events were considered unrelated to idebenone treatment.

Evidence gaps and limitations

There were a number of limitations in the evidence base. Although RHODOS provided randomised controlled evidence on the efficacy of idebenone over a 24-week period, there is limited evidence on the long-term effects of idebenone. The available evidence was taken from OFU data which was based on a single visit (approx. 30 months after the completion of RHODOS), where patients had not been receiving further treatment with idebenone between the completion of RHODOS and their follow-up visit and the EAP where patients with LHON were prescribed idebenone on an individual basis for a longer duration, under the care and discretion of their treating physician. However, that data can provide useful information on the efficacy of idebenone in clinical practice.

The EPAR considered several limitations to the outcome measures. The primary outcome (best recovery/ least worsening of VA) may not necessarily reflect changes in VA relevant to the patient's overall ability to see. The key secondary end-point of the change from baseline in patients best VA compared VA in the patients better seeing eye at baseline with the VA in the patients better seeing eye at Week 24 even if the better seeing eye was not the same one at Week 24 as baseline.

The EPAR noted there were a number of areas of potential bias influencing the interpretation of the evidence. The exclusion of one patient from the placebo group, in the mITT analyses created uncertainties in the robustness of the RHODOS data and resulted in a considerable increase of the between-group differences. Further sources of bias were drawn from the observational findings: patients included in the single-visit OFU had previously participated in RHODOS, but did not receive treatment following the completion of the study, and in data obtained from the EAP, the EPAR noted it could not conclude with certainty that bias had not been introduced due to the open-label, uncontrolled nature of the data collection. Limitations also arose in considering data in the case record survey, mainly because this was based on a retrospective analysis of patient records, provided differences in VA measurements and data from patients receiving no treatment or varying doses of idebenone medication.

Further uncertainties in the data arose from the interpretation of the RHODOS-OFU results. The EPAR stated the limited intermediate data collection between the end of RHODOS to the OFU visit contributed to uncertainties in interpretation of the analyses which meant the detailed time courses for changes in both treatment arms from the end of RHODOS to the OFU visit were not known.

RHODOS provided evidence for the use of idebenone in people with LHON aged 14 years or over, however limited evidence is available from the case record survey of idebenone use in people aged younger than 14 years of age. The decision made by the EMA during the regulatory process was that the availability of this data justified the consideration of adolescents in general rather than providing a cut-off of aged 14-years, however, the summary of product characteristics has noted that it is not known if idebenone is safe or works in patients under 12 years of age

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Abbreviations

Term	Definition
logMAR	logarithm of the minimal angle of resolution
CRR	Clinically relevant recovery (of visual acuity)
sCRR	Spontaneous clinically relevant recovery (of visual acuity)
CRS	Clinically relevant stabilization (of visual acuity)
RHODOS	Rescue of Hereditary Optic Disease Outpatient Study
EAP	Expanded Access Programme
EPAR	European Public Assessment Report
OFU	Open label follow-up

Medical definitions

Term	Definition
LHON	Leber's Hereditary Optic Neuropathy
mtDNA	Mitochondrial DNA
ETDRS	Early treatment diabetic retinopathy study
VA	Visual acuity
AE	Adverse event
Nadir	The lowest reported value

1 Introduction

Disease background

1.1 Leber's hereditary optic neuropathy (LHON) is a rare maternally-inherited genetic disease, which causes visual impairment. LHON is caused by mutations in mitochondrial DNA (the part of cells that creates the energy needed for them to function), which damages the cells in the retina of the eye.

1.2 Vision problems initially start with a painless blurring or clouding of central vision which can occur either simultaneously or one after the other in both eyes, but will eventually progress to blindness in both eyes. Progression can be very rapid (over a period of months) or may take longer to progress (over a number of years) but around 97% of people with LHON will have both eyes affected within one year of diagnosis (***Meyerson, 2015***). Although only females can pass on the LHON genetic mutation to their children, both males and females can be carriers. An average of 50% of males and 15% of females with a LHON mutation will lose vision in their lifetime (***United Mitochondrial Disease Foundation***). Onset can occur at any age and for both males and females, although mostly occurs in males aged 15-35 years (***Fraser, 2010***).

Focus of review

1.3 In line with the marketing authorisation, the focus of this review is on idebenone for the 'treatment of visual impairment in adults and adolescents with LHON'. Although the age of 'adolescents' is not defined in the licensed wording, the statement of product characteristics states the safety and efficacy of idebenone in people with LHON under 12 years of age "have not yet been established".

Epidemiology and needs assessment

1.4 The prevalence of LHON in England has been estimated to be 3.22 to 4.4 per 100,000, based on two studies in North-East England (Man et al. 2003

and Gorman et al. 2015). Based on the predicted population of England in 2018 of 55,997,700, this equates to a prevalence of 2,072 people with LHON in England.

1.5 Although there are no published incidence figures available for LHON, based on an average age of onset between 20 and 30 years, a life expectancy of 80 years and an average disease duration of 55 years, the incidence in England is estimated to be 38 patients per year.

Product overview

Mode of action

1.6 Idebenone is a type of drug known as a short chain benzoquinone, and an antioxidant agent that acts on mitochondria (the energy producing part of cells necessary for cells to function). In people with LHON, genetic mutations (or defects) in the mitochondria means the mitochondria cannot properly generate energy. This produces free radicals which damage the cells of the eye which are needed for vision. It is thought that idebenone will activate viable-but-inactive retinal ganglion cells, which can enable recovery of vision in patients who have experienced vision loss and help prevent patients from becoming blind.

Regulatory status

Idebenone was granted a marketing authorisation by the European Medicines Agency (EMA) on the 08th September 2015.

Dosing information

1.7 Idebenone is available in 150 mg film-coated tablets.

The recommended dose is 900 mg per day (300 mg, 3 times a day) to be taken orally, with food. For further details of dosing please see the summary of product characteristics.

Treatment pathway and current practice

Current treatment options for people with LHON are limited to best supportive care (BSC). Idebenone is the only licensed therapy for the treatment of visual impairment in adolescent and adult patients with LHON.

2 Evidence

Literature search

2.1 A literature search was done, which identified 144 references (see appendix 1 for search strategy). These references were screened using their titles and abstracts and 17 full text references were obtained and assessed for relevance. Full text inclusion and exclusion criteria were applied to the identified studies and 2 studies from the search were included in the clinical evidence review (Klopstock et al. 2011, and Rudolph et al. 2013). Please see appendix 2 for inclusion criteria and a list of studies excluded at full text with reasons.

Evidence was also drawn specifically from the European Public Assessment Report (EPAR), which identified evidence from two more additional records.

Overview of included studies

2.2 One randomised controlled trial (RCT) was identified from the search, Klopstock et al. 2011 (RHODOS). This was supported by a post-hoc sub-analysis of a small population completing the RHODOS trial, focusing on colour sensitivity (Rudolph et al. 2013). Further evidence which was originally included in the European Public Assessment Record (EPAR) and considered by the European Medicines Agency during the regulatory process was included in this evidence review. This included an additional single time-point, open-label follow-up study of people completing the RHODOS study (RHODOS-OFU); and a natural history case record survey of 383 cases (provided by the company as evidence to support the

regulatory process). Other evidence which was originally included in the EPAR is also included in this evidence review. This includes the findings from an expanded access programme (EAP) which reported on patients' clinical experience of using idebenone on a longer term-basis. There was no control group, but this study provides evidence relating to the proportion of people receiving idebenone who achieved a clinically relevant recovery (CRR). Data from the original cut-off period (prior to the EMA marketing application) was reported in the EPAR. A summary of the characteristics of the included studies is shown in table 1 (please see evidence tables for full details).

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
Klopstock et al. 2011 (phase II RCT - RHODOS trial) [a]	People aged ≥14 and < 65 years with onset of vision loss in at least one eye due to LHON (≤ 5 years) and confirmation of either G11778A, T14484C or G3460A LHON mtDNA mutations (N=85; idebenone, n=55; placebo n=30)	Idebenone (900 mg per day) vs placebo	Best recovery/least worsening of logMAR visual acuity between baseline and week 24
Rudolph et al. 2013 (sub analysis of RHODOS trial)	People aged ≥14 and < 65 years with onset of vision loss in at least one eye due to LHON (≤ 5 years) and confirmation of either G11778A, T14484C or G3460A LHON mtDNA mutations (n=39[b];	Idebenone (900 mg per day) vs placebo	Change in colour contrast sensitivity between baseline and week 24

	idebenone n=28; placebo n=11)		
Open label uncontrolled expanded access program EAP- reported in EPAR only)	People with LHON and carrying 1 of the 3 major LHON mtDNA mutations and within 12 months of disease onset in most recently affected eye (n=63)	Idebenone (typical dosing at 900mg per day) vs no comparator	Proportion of patients with clinically relevant recovery (CRR) of visual acuity from the lowest point
RHODOS- OFU single visit observational follow-up (reported in EPAR only)	People originally taking part in RHODOS (n=60) in both idebenone (n=41) and placebo (n=19) groups	Not receiving idebenone treatment but 5 people reported using it between end of RHODOS and RHODOS-OFU visit. 3 reported use at 900 mg/day, otherwise unreported dose	Mean change in best VA at time of OFU visit Single analysis (median 30 months; range: 20.9 to 42.5 from week 24 of RHODOS to time of follow-up visit)
Case record survey of 383 cases of VA data taken from existing medical records (from EPAR)	People with a molecular diagnosis of LHON and being seen in participating European Vision Institute Clinical Research Network member centres, and LHON-treating centres in the EAP. 11 centres provided CRS data	Either receiving or not receiving idebenone Average dose 520 mg/day (median 405 mg/day; range 60-900 mg/day).	VA as a function of time since onset of symptoms Mean duration of therapy 1.5 years

[a] additional data also reported in the EPAR)

[b] Rudolph et al. (2013) was a post hoc sub analysis of a sub population completing the RHODOS trial

Abbreviations: mtDNA; mitochondrial DNA; logMAR = logarithm of the minimal angle of resolution; RCT; Randomised controlled trial; EAP; Expanded Access Programme EPAR; European Public Assessment Report

Key outcomes

2.3 The key outcomes identified in the scope are discussed below for effectiveness and safety. Table 3 below provides a grade of evidence summary of key outcomes (see appendix 5 for the details of grading evidence). The more detailed evidence tables and results for each study are in appendices 3 and 4.

Effectiveness

Visual acuity:

2.4 The best evidence comes from the phase II double-blind randomised, controlled RHODOS trial. The primary outcome reported in that study was best recovery/least worsening of visual acuity (VA) at 24 weeks (study end-point), for people with improving VA in either left or right eyes and was identified using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart and expressed using logarithm of the minimal angle of resolution (logMAR) values. For people whose VA did not improve between baseline and the 24-weeks end-point, the change in VA showing the least worsening was regarded as best recovery. RHODOS reported that logMAR values ≥ 1.0 in both eyes corresponded to legal blindness. The EPAR noted that using the logMAR scale allows results over a large range of visual abilities to be quantified from 0.0 (normal vision) up to 1.68 able to read only 1 large letter correctly at 1 metre distance. Where change from baseline scores were reported in the studies, a positive logMAR value (showing an increasing logMAR) indicated worsening and a negative logMAR value (showing a decreasing logMAR) indicated improvement.

2.5 In RHODOS the logMAR between baseline and 24-week end-point (best recovery/least worsening of VA) for all people receiving idebenone improved with a mean logMAR value of -0.135 (95% confidence intervals (CI) -0.216 to -0.054). This equated to an improvement of 6 letters on the ETDRS chart. For people receiving placebo, the mean change from baseline also improved, with a logMAR value -0.071 (95%CI -0.176 to

0.034), equating to an improvement of 3 letters on the ETDRS chart. The estimated mean difference between groups was not statistically significant (logMAR = -0.064, 95% CI: -0.184 to 0.055); equating to a 3-letter change, p = 0.291).

2.6 The secondary outcomes in RHODOS were the change in best VA at baseline, the change of VA of the best eye at baseline and the change from baseline in VA of both eyes. Although the reported change in best VA and in VA of the best eye at baseline did not reach statistical significance (Best VA: Idebenone: change in logMAR: -0.035; 95% CI: -0.126 to 0.055, + 1 letter; Placebo: logMAR + 0.085; 95% CI: -0.032 to 0.203, - 4 letters; difference between groups: logMAR -0.120; 95% CI: -0.255, 0.014; 6 letters, p = 0.078); VA of best eye: idebenone: change in logMAR:- 0.030; 95% CI: -0.120 to 0.060, number of letters not reported; placebo: logMAR + 0.098; 95% CI: -0.020 to 0.215, number of letters not reported; estimated difference between groups: logMAR -0.128; 95% CI: -0.262 to 0.006; letter change not reported, p = 0.061), there was a statistically significant improvement from baseline in VA of both eyes combined for idebenone (change in logMAR -0.054; 95% CI= -0.114 to 0.005, number of letters not reported) compared with placebo (logMAR 0.046; 95% CI: -0.032 to 0.123, number of letters not reported; estimated difference between groups = logMAR -0.100; 95% CI: -0.188 to -0.012, letter change not reported; p = 0.026).

2.7 A sub-analysis of patients with discordant VA at baseline (that is, people whose visual acuity between their eyes was different at baseline, with a difference of logMAR >0.2 between eyes) was carried out. Statistically significant improvements in visual acuity for idebenone compared with placebo were found from baseline to 24 weeks for the following:

- Change in best recovery of visual acuity (logMAR = -0.285; 95% CI: -0.502 to -0.068; p = 0.01).
- Change in best visual acuity (difference between groups: logMAR = -0.421; 95% CI: -0.692 to -0.150; p = 0.003)

- Change in visual acuity of the patient's best eye (difference between groups: logMAR = -0.415; 95% CI: -0.686 to -0.144; p = 0.003),
- Change in visual acuity for all eyes (difference between treatment groups: (logMAR = -0.348; 95% CI: -0.519 to -0.176; p = 0.0001).

2.8 However, there were no statistically significant differences in any outcomes among people with concordant visual acuity (estimated difference between treatment groups: logMAR= 0.056 (95% CI: -0.091 to + 0.202; p = 0.452) for best recovery in visual acuity; logMAR = 0.037 (95% CI: -0.107 to + 0.180; p = 0.613) for the best visual acuity; logMAR + 0.022 (95% CI: -0.120 to + 0.165; P = 0.757) for change in visual acuity of the patient's best eye and logMAR + 0.028 (95% CI: -0.070 to + 0.125; p = 0.577) when data for all eyes was combined.

2.9 The EPAR reported on a further analysis of this data based on the modified ITT (mITT) population. The mITT population was the same as the ITT population (used in the previous reported efficacy analysis) but for visual acuity data excluded one patient who had been randomised to placebo and was considered as a natural history confounder due to an on-going spontaneous recovery of vision at the time of randomisation into the study. When analysis was based on the mITT population, the difference between treatment groups for all patients was still showing as not statistically significant for the primary outcome of change in logMAR between baseline and 24-week end-point for best recovery/ least worsening VA (difference between groups = -0.100 (95%CI -0.214; -0.014; p=0.0862). However, the results for the secondary outcome (change in best VA at 24 weeks) resulted in a statistically significant difference between groups in favour of idebenone (logMAR =-0.160 (95%CI = -0.289 to -0.031), 8 letters difference, p=0.015.

2.10 A further sub-analysis (based on mutation type) only reported in the EPAR, but based on the mITT population analysis found the differences between treatment groups for both the primary outcome and main secondary outcome (change in best VA at 24 weeks) reported statistically

significant differences between treatment groups in favour of idebenone for the sub group of patients with the G11778A mutation (best recovery/ least worsening difference between groups at 24 weeks = logMAR -0.148 (± 0.073 standard error), p=0.047) and for the main secondary outcome (change in best VA, difference between groups at 24 weeks = logMAR – 0.198 (± 0.083 standard error), p=0.019.

2.11 The RHODOS trial identified responders to treatment by performing several responder analyses. The number of responders whose VA changed from baseline to 24-week end-point were identified by counting the number of patients and eyes that changed by a logMAR value ≥0.2 (≥10 ETDRS chart letters). There was no statistically significant difference between groups in the number of people and eyes responding to treatment in any of the 4 main outcomes:(improvement in best recovery/least worsening in VA; p=0.231; improvement in best VA: p=0.420; improvement in VA of all eyes; p=0.131; worsening in VA of all eyes; p=0.075) when all people contributing to the efficacy analysis were assessed. There was, however, a 45% difference in the number of responders for the best recovery/least worsening of VA in the subgroup of people with discordant VA at baseline (p = 0.024); and a 32.5% difference for this subgroup when the total number of eyes responding to treatment was assessed (p = 0.011) for this sub-population. When comparing the responder analysis for the sub-population of patients unable to read any letters on the chart at baseline (classified as 'off-chart patients'), 20% of the eyes of the patients receiving idebenone were able to read at least one full line on the chart at Week 24, whereas none of the patients in the placebo group showed this improvement (p = 0.008). The responder analyses also found a statistically significant difference between groups in favour of idebenone (0 out of 6 people) compared with placebo 2 out of 2 people) in the sub-population of people with best corrected vision (logMAR ≤0.5) in at least one eye at baseline, whose vision did not deteriorate to that of legal blindness (logMAR ≥1.0) at 24 weeks (p=0.036).

2.12 A further responder analyses, based entirely on the mITT population was reported in the EPAR. The proportion of people who achieved a clinically relevant recovery (CRR) was defined as people who had an improvement of at least logMAR 0.2 if “on-chart” VA at baseline, or an improvement from “off-chart” VA to at least logMAR 1.6 if off-chart VA at baseline. The EPAR acknowledged the CRR was a valuable marker for assessing treatment benefit, Results found 16 people of the idebenone group achieved a CRR at 24 weeks (21 eyes; 19.8% of eyes) equating to an 11 letter change (-0.23 logMAR) in total, compared with 2 people achieving a CRR in the placebo group (2 eyes; 3.6%) equating to 18 letter change (-0.37 logMAR) in total (p=0.0234), the result based on the proportion of eyes was also statistically significant (p=0.0041). The EPAR presents a comparison of the proportions of idebenone and placebo-controlled patients in the mITT population who recovered from their VA nadir (see Table 2 below). A statistically significant difference in favour of idebenone was seen for patients presenting with recovery (p=0.0321). Statistical significance was also reached in patients with a disease duration ≥1 year, but there was no significant between-treatment difference for disease duration <1 year.

Table 2: Proportion of people with CRR from nadir at 24 weeks (mITT population)

	Idebenone n=53	**Placebo n=28**	**p-value**
Recovered from nadir (all patients)	18 of 53 (34.0%)	3 of 28 (10.7%)	P=0.0321
Recovered from nadir (duration of LHON <1 year)	5 of 19 (26.3%)	1 of 9 (11.1%)	P=0.6296

Recovered from nadir (duration of LHON ≥ 1 year)	13 of 34 (38.2%)	2 of 19 (10.5%)	P=0.0545

2.13 There was no statistically significant difference in the proportion of people with a clinically relevant worsening (CRW) in best VA (change from baseline of ≤1.6 logMAR to 'off chart' or change of <logMAR 0.2 if 'on-chart') which was recorded in 2 people (3.8%) in idebenone group and 2 people (7.1%) placebo (p=0.6058). The difference between treatment groups in time to achieving a CRR was also reported as statistically significant in favour of the idebenone group (median to CRR = 42.4 months from onset) compared with placebo (median time to CRR not reached), p= 0.0133.

2.14 The EPAR also reported on an observational single visit follow-up study (RHODOS-OFU), which examined the change in VA of 60 of the 85 patients who had previously participated in RHODOS [median time of 30 months (range: 20.9 to 42.5 months; 131 weeks) from week 24 last visit of RHODOS to the time of the follow-up visit. Patients did not receive treatment during the follow-up period between RHODOS end-point to the start of RHODOS-OFU. The mean change in best VA compared the results of the current VA with that observed at original baseline and after 24 weeks of treatment in RHODOS. Best VA at the RHODOS-OFU visit was slightly worse than at baseline in patients in the placebo group (mean change in logMAR = +0.039, corresponding to a worsening of 1 letter) whereas best VA improved in the idebenone group (mean change in logMAR = -0.134, corresponding to an improvement of 6 letters). The difference between idebenone and placebo groups was not statistically significant at OFU visit (difference between groups logMAR= -0.173 (95%CI = -0.370 to 0.024; 8 letters; p=0.0845). No statistical differences between groups were observed for baseline to week-24 of RHODOS (logMAR= -0.175 (95%CI= -0.375 to 0.024; 8 letters; p=0.0844) or week-

24 of RHODOS to the OFU (logMAR = +0.002 (95%CI = -0.190 to 0.195; 0 letters; p= 0.9819).

2.15 Supportive evidence on the longitudinal effects of idebenone in patients with LHON was included whereby idebenone was prescribed in a multi-centre open-label- uncontrolled way to 93 people on a named patient access basis in an Expanded Access Programme (EAP), which commenced in 2011. VA data was assessed using ETDRS charts and logMAR values, or converted from standard Snellen notation to logMAR values. The EPAR reported upon data recorded at time of last VA assessment (at a clinical cut-off date of March 2015). The EPAR reported the main inclusion criteria for the EAP was a confirmed LHON mtDNA mutation and onset of vision loss in the second eye of less than 12 months prior to the date of the baseline visit. Patients were given access to idebenone (generally receiving 900 mg per day; 300 mg three times a day) although treatment duration and dosing was at the discretion of the treating physician.

2.16 At the March 2015 cut-off date, the EPAR reported the mean treatment duration at time of cut-off was 15.4 (range 2.8 to 36.2) months, and at that time, 34 out of 69 patients (49.3%) and 55 out of 138 eyes (39.9%) experienced a clinically relevant recovery (CRR) from VA at their lowest reported point to their last assessment.

2.17 The EPAR provided additional data regarding the natural course of vision loss and recovery in patients with a genetically confirmed diagnosis of LHON. Historically documented VA data from existing medical records were collected from 11 centres (10 European and 1 in the USA). Each centre was asked to provide historical case record data from all LHON patients (with molecular diagnosis) on file without pre-selection. This provided a case record survey of 383 case records.

2.18 For patients receiving idebenone the EPAR reports the CRR of VA from lowest reported point was seen in 24 of 48 patients (50%) and 38 of 96 eyes (39.6%). In these patients, the mean time from onset to CRR was

16.2 (range 1.9 – 39.4) months. The mean magnitude of the best CRR (best recovering eye in each patient), was 38 (range 8 to 82) letters. Of the 26 patients who had VA logMAR <1.0 at presentation, 7 (26.9%) still had VA logMAR <1.0 at outcome. Of the 39 patients with on-chart vision at presentation 14 patients (35.9%) and 29 of 71 eyes (40.8%) did not have clinically relevant worsening (CRW) in VA of at least one eye.

2.19 Of the patients who were not receiving idebenone treatment, 23 out of 74 patients (31.1%) and 36 out of 148 eyes (24.4%) experienced a spontaneous clinically relevant recovery (sCRR) in at least one eye and 13 of these patients improved with both eyes. The proportions of patients with sCRR appeared similar in patients with time since onset at presentation of ≤6 months (31.8%, 20/63) and >6-12 months (33.3%, 3/9). Analysis of the proportions of patients with sCRR by mtDNA mutation showed that higher proportions of sCRR were observed in patients carrying the G3460A (50.0%, 6/12) and T14484C (42.9%, 3/7) mutations compared with patients carrying the G11778A mutation (25.5%, 14/55).

2.20 The EPAR also reported on data from two retrospective studies. Mashima et al. (2000) and Carelli et al. (2011) reported the proportion of patients with medically-relevant improvement of VA for patients with the G11778A mtDNA mutation (vast majority of patients living in Europe) and disease onset ≤ 1year before treatment as follows: Responders with VA recovery ≥ 0.3 (decimal acuity) in patients treated with idebenone was 26.4% (4 of 11 patients) compared with 10.0% (1 of 10 patients) in the untreated comparator group (Mashima et al. 2000). Responders with VA improvement by 2 lines on a Snellen Chart or from “off-chart” to “on-chart” vision in patients treated with idebenone was 46.7% (14 of 30 patients) compared with 23.3% (10 of 43 patients) in the untreated comparator group (Carelli et al. 2011).

Colour contrast sensitivity

2.21 A sub-population of the RHODOS trial (39 participants at one centre) were assessed for colour-contrast sensitivity. Red–green (protan) and blue–

yellow (tritan) colour confusion was identified using computer graphics. There was a statistically significant improvement in the tritan colour contrast in the idebenone group at 12 weeks (difference between groups: -14.51%; 95% CI: -24.19 to -4.83; p = 0.004) and 24 weeks (difference between groups: -13.63%; 95% CI: -23.61 to -3.66; p = 0.008). The changes in protan colour contrast between baseline and 24 weeks did, however, not reach statistical significance [Difference between groups = -3.9% (CIs not reported; p=0.239)].

2.22 Rudolph et al. (2013) further considered the changes in colour-contrast sensitivity in a post-hoc sub-analysis of the 39 participants originally assessed. People with discordant VA (a difference of logMAR ≥0.2 corresponding to 2 lines on the ETDRS chart between eyes at baseline) taking placebo showed a statistically significantly larger decline in protan colour contrast sensitivity when compared with idebenone (estimated difference between patients receiving idebenone and placebo treatment = mean -16.6% (± 7.1 standard error) p=0.022 at 12 weeks and mean -13.5% (± 7.2 standard error) p=0.067 at 24 weeks) and for the change in tritan colour contrast sensitivity (estimated difference between patients receiving idebenone and placebo treatment = mean -12.7% (± 6.6 standard error) p=0.060 at 12 weeks and -20.4% (± 6.9) p=0.005 at 24 weeks). For patients with discordant VA, change in VA and change in colour contrast sensitivity from baseline to week 24 were correlated (correlation between change in VA and protan: R^2 = 0.532, p= 0.001; correlation between change in VA and tritan: R^2 = 0.358, p= 0.001).

2.23 Rudolph et al. (2013) also found a statistically significant difference in tritan colour contrast in patients younger than 30 years in favour of idebenone compared with placebo (estimated difference between idebenone and placebo groups = -19.2 (6.6) p=0.005 at 12 weeks and -17.6 (6.7) p=0.010 at 24 weeks). The results were not statistically significant for protan colour contrast (estimated difference between idebenone and placebo groups = -3.4 (4.0) p=0.400 at 12 weeks and -2.8 (4.1) p=0.486 at 24 weeks).

2.24 The change from baseline in protan colour contrast in patients aged 30 years or older only showed statistically significant differences between treatment groups at 12 weeks follow-up (estimated difference between idebenone and placebo groups = -15.3 (6.9) p=0.032) but did not reach statistical significance at 24 weeks follow-up for protan colour contrast [(estimated difference between idebenone and placebo groups = -4.4 (7.6) p=0.56]. The difference in treatment groups in change from baseline in tritan colour contrast in this sub-population did not reach statistical significance at either 12 or 24 weeks

2.25 The change from baseline in colour contrast sensitivity in patients with up to 1 years diagnosis did not reach statistical significance in either tritan colour contrast sensitivity (estimated difference between idebenone and placebo groups = -16.4 (11.7) p=0.170 at 12 weeks and -10.2 (12.6) p=0.423 at 24 weeks), or in protan colour contrast sensitivity (estimated difference between idebenone and placebo groups = -6.3 (6.8) p=0.356 at 12 weeks and 2.0 (7.5) p=0.785 at 24 weeks. Whereas the change from baseline in people with more than 1 year diagnosis only showed a statistically significant difference in tritan colour contrast sensitivity (estimated difference between groups = -8.5 (3.7) p=0.026 at 12 weeks and 11.6 (3.7) p=0.003 at 24 weeks). The change in protan colour contrast sensitivity did not reach statistical significance (estimated difference between groups = -1.3 (2.8) p=0.655 at 12 weeks and -3.3 (2.8) p=0.242 at 24 weeks).

Retinal nerve fibre layer thickness

2.26 In RHODOS, retinal nerve fibre layer thickness was assessed in 41 patients by optical coherence tomography. The authors stated there was a ‘trend towards maintaining’ retinal nerve fibre layer thickness in the idebenone group in superior, nasal and inferior quadrants, among patients with 46 months disease history, although, no formal statistical analysis was carried out due to the small sample size.

Health related quality of life

2.27 The EPAR reported the health-related quality of life assessment in RHODOS. The Visual Function (VF)-14 tool was used to obtain these outcomes. The Visual Function Index (VF-14) is a brief (18 questions) self-reported questionnaire designed to measure functional impairment and covers 14 aspects of visual function. The scores are graded using a 0 to 4 point scale and multiplied by 25 to give a value between 0 to 100, where a lower score indicates the person has more difficulty in doing all applicable activities because of their vision.

2.28 There was no statistically significant difference between treatment groups in change of VF-14 score at 24 weeks follow-up (estimated mean treatment difference = -1.37; 95%CI -6.25 to 3.51; p=0.577).

2.29 The EPAR reported that VF-14 data were available for 57 patients taking part in the RHODOS-OFU. The EPAR noted that the overall changes between VF-14 score recorded during RHODOS and RHODOS-OFU were small and differences between idebenone and placebo groups were not statistically significant. There was a small worsening in the idebenone group (-1.7%) compared to a small improvement in the placebo group (2.4%; p=0.205) for the entire period between RHODOS baseline to the RHODOS-OFU.

2.30 The EPAR also reported the findings of the use of the Clinician's Global Impression of Change (CGIC) score during RHODOS. The CGIC is a 3-item observer-rated scale that measures global improvement or change in illness experience . It is rated on a 7-point scale, with the severity of illness scale using a range of responses. Scores range from 1 (very much improved) through to 7 (very much worse).

2.31 The change from baseline in CGIC scores was determined at 24 weeks. Although statistical analysis was not reported, the EPAR noted that 12 participants (22.6%) receiving idebenone; compared with 7 participants (24.1%) receiving placebo reported improvement in overall CGIC scores. Forty-three participants (81.1%) receiving idebenone compared with 24

participants (82.8%) receiving placebo reported less fatigue/ no change in fatigue levels at 24 weeks follow-up.

2.32 General energy levels were assessed by a visual-analogue scale (VAS). The EPAR reported no statistically significant differences in change in VAS score at 24 weeks (estimated mean treatment difference = - 1.80 points; 95% CI 11.37 to 7.77 points; p=0.709).

Safety and tolerability

2.33 All 85 participants in RHODOS were assessed for safety and tolerability, with one patient in each treatment arm discontinuing due to an adverse event (AE). The authors reported that the nature, severity and frequency of the observed AEs were indistinguishable between the treatment groups. Two serious AEs were reported. One AE was in the idebenone group (an infected epidermal cyst) and 1 in the placebo group (a case of epistaxis) although both were not considered to be due to the treatment received.

2.34 The European Public Assessment Report noted that 89% of people receiving idebenone and 87% of people receiving placebo reported at least one AE. The majority of AEs were mild or moderate in intensity including headache reported in 13 people (23.6%) receiving idebenone and 6 people (20%) receiving placebo and nasopharyngitis in 14 people (25.5%) receiving idebenone and in 5 people (16.7%) receiving placebo. The EPAR also reported no deaths occurred in the RHODOS study.

In the EAP 17 AEs had been reported in 10 patients at the time of cut off. The most frequently reported AE was mild diarrhoea. The severity of reported AEs were classified as mild (65%), moderate (24%) or unknown (11%)

Evidence gaps and limitations

2.35 There were a number of limitations in the evidence base. RHODOS was of relatively short duration (24 weeks) and a small trial (limited to 85 participants). Therefore only short term outcomes are available in a controlled environment and this may not have been long enough to

assess the full benefits of idebenone treatment. The primary outcome of RHODOS was not fulfilled, and although the authors attempted to address areas of uncertainty by completing sub and post hoc analyses, some uncertainty surrounds the main findings (which were drawn from a heterogeneous population). RHODOS is however the first trial of its kind, in the orphan disease of people with LHON. Although the data available on a longer-term basis (from the EAP and case records) was not conducted under a controlled environment, this data can provide useful information on the efficacy of idebenone in clinical practice and on the rate of disease progression and outcomes in patients who do not receive idebenone treatment.

The EPAR noted that assessment of clinical effectiveness was mainly based on changes in VA data and considered several limitations to the outcome measures. The primary outcome (best recovery/ least worsening of VA) may not necessarily reflect changes in VA relevant to the patient's overall ability to see. The key secondary end-point of the change from baseline in patients best VA was thought to complement the findings from the primary outcome; this compared VA in the patients better seeing eye at baseline with the VA in the patients better seeing eye at Week 24 even if the better seeing eye was not the same one at Week 24 as baseline. When considering the relevance of these outcomes, it should be considered that VA is thought to be a narrow way to define sight. Although best recovery in either eye may be considered a satisfactory outcome, the main focus in determining benefit will be at an individual level, marginal improvements of VA in one eye can have a substantive change to an individual.

Although RHODOS provided randomised controlled evidence on the efficacy of idebenone over a 24-week period, there is limited evidence on the long-term effects of idebenone. The available evidence was taken from OFU data which was based on a single visit (approx. 30 months after the completion of RHODOS), where patients had not been receiving further treatment with idebenone between the completion of RHODOS

and their follow-up visit and the EAP where patients with LHON were prescribed idebenone on an individual basis for a longer duration, under the care and discretion of their treating physician

The EPAR noted there were several areas of potential bias influencing the interpretation of the evidence. The EPAR stated that the exclusion of one patient from the placebo group, in the mITT analyses created uncertainties in the robustness of the RHODOS data and resulted in a considerable increase of the between-group differences. In addition, given the potential of spontaneous recovery in LHON's disease, there was a risk of over-estimating the effect of idebenone. Further sources of bias were drawn from the observational findings: patients included in the single-visit OFU had previously participated in RHODOS, but did not receive treatment following the completion of the study, and in data obtained from the EAP, the EPAR noted it could not conclude with certainty that bias had not been introduced due to the open-label, uncontrolled nature of the data collection. Limitations also arose in considering data in the case record survey, mainly because this was based on a retrospective analysis of patient records, provided differences in VA measurements and data from patients receiving no treatment or varying doses of idebenone medication.

Further uncertainties in the data arose from the interpretation of the RHODOS-OFU results. The EPAR stated that the similar improvements in VA observed for the idebenone and the placebo group in RHODOS-OFU after a mean time of 2.5 years from Week 24 in RHODOS, suggested the benefit of 6 months treatment with idebenone may persist even after treatment was withdrawn. However, the EPAR also stated the limited intermediate data collection between the end of RHODOS to the OFU visit contributed to uncertainties in this interpretation: The EPAR states visual improvement was mainly seen in people with a shorter disease history, and also suggested the course of LHON means people with LHON can adapt by using peripheral vision instead of foveal vision for object recognition, as a result, the detailed time courses for changes in

both treatment arms from the end of RHODOS to the OFU visit were not known.

RHODOS provided evidence for the use of idebenone in people with LHON aged 14 years or over, however limited evidence is available from the case record survey of idebenone use in people aged younger than 14 years of age. The decision made by the EMA during the regulatory process was that the availability of this data justified the consideration of adolescents in general rather than providing a cut-off of aged 14-years, however, the summary of product characteristics has noted that it is not known if idebenone is safe or works in patients under 12 years of age.

Table 3 Grade of evidence for key outcomes

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
Visual acuity	Klopstock et al. 2011 (RHODOS)	7/10	Directly applicable	B	Visual acuity measures clarity of vision. In all studies, visual acuity was measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart or converted values from Snellen charts. Both charts are used to determine the number of letters a person can read on a standardised chart. The number of letters was expressed using the logarithm of the minimal angle of resolution (logMAR) values. A + logMAR value indicated worsening and a – logMAR value indicates improvement. The best evidence came from a 24-week phase II randomised placebo-controlled trial (RHODOS), n=85 people aged 14 years and older with LHON. The primary outcome of best recovery/ least worsening in visual acuity showed a mean number of letter improvement at 24 weeks follow up of 6 for idebenone and 3 for placebo, however this was not statistically significant (logMAR = -0.064 (with a 95% CI: -0.184 to 0.055, p=0.291). The secondary outcomes in RHODOS were the change from baseline in best VA, as well as VA of best eye (not statistically significant) and both eyes (statistically significant improvement for idebenone compared with placebo, estimated difference between groups = logMAR -0.100; 95% CI: -0.188 to -0.012; p = 0.026). Furthermore, results from a post-hoc sub-analysis showed that among people with discordant VA at baseline (a difference of logMAR >0.2 between eyes) a statistically significant improvement for idebenone compared with placebo was found for all primary and secondary outcomes: best recovery/ least worsening (logMAR = -0.285; 95% CI: -0.502 to -0.068; p = 0.01); best visual acuity (logMAR = -0.421; 95% CI: -0.692 to -0.150; p = 0.003;); change in visual acuity of the patient's best eye (logMAR = -0.415; 95% CI: -0.686 to -0.144; p = 0.003), and for all eyes (logMAR= -0.348; 95% CI: -0.519 to -0.176; p = 0.0001). A statistically significant difference between groups, in favour of idebenone was found in the proportion of eyes whose VA achieved a CRR at end-point, in 21 eyes (19.8%) in 16 people receiving idebenone and in 2 eyes (3.6%) in 2 people in placebo (p=0.0041). There were no statistically significant differences between groups in the proportion of people with a clinically relevant worsening (CRW). The results of an expanded access program (EAP) where people were prescribes idebenone on a named patient basis, reported in the EPAR reported the mean treatment duration at
	EAP (march 2015 data cut off, reported in EPAR only)				

					time of cut-off was 15.4 (range 2.8 to 36.2) months, and at that time, 34 out of 69 patients (49.3%) and 55 out of 138 eyes (39.9%) experienced a clinically relevant recovery (CRR) from VA at their lowest reported point to their last assessment The results of an open label follow-up visit (RHODOS-OFU), where people did not receive further treatment with idebenone found no difference between groups in VA of best eye from either baseline or endpoint of RHODOS to time of OFU visit (a mean of 30 months). The EPAR stated that the "in-between group difference was maintained, suggesting that the benefit obtained with idebenone after 6 months treatment persisted even after withdrawal of treatment". Results suggest that overall, there were few statistically significant VA improvements in RHODOS for the whole population receiving idebenone compared with placebo, however, the proportion of eyes achieving a clinically relevant recovery (CRR) was statistically significant in favour of people receiving idebenone. In addition, results from sub-analyses suggest there may be some beneficial effect of idebenone in stabilising or improving VA in subgroups, particularly for people with discordant VA. Visual acuity is thought to be a narrow way to define sight. VA charts are in general, thought to be blunt instruments for measuring the impact of visual impairment. The EPAR stated the primary outcome (best recovery/ least worsening) would not necessarily reflect changes in VA relevant to overall ability to see, but it did recognise that CRR was a valuable marker for assessing treatment benefit. When vision is poor, marginal improvements of VA in some may have a substantive change in ability to see or function. Results should be treated with caution because the RHODOS trial was a phase II design of a relatively small population of people at various stages of disease progression with a short follow-up and therefore provides limited evidence on the long-term benefits of idebenone therapy. The EPAR stated "there was a risk of over-estimating the effect of idebenone" because of potential for spontaneous recovery in LHON" and reliance on the mITT analysis could lead to "uncertainties in the robustness of the RHODOS data" because the exclusion of the patient deemed a confounder resulted in considerable increase of the between-group differences.
Colour contrast sensitivity	Klopstock et al. 2011 (RHODOS)	7/10	Directly applicable	A	Colour contrast sensitivity tests measure the ability to distinguish between finer increments of light versus dark increments (contrast). This was measured using assessment of protan (red-green) and tritan (blue-yellow) colour vision. The difference between treatment groups was presented as a percentage change, where a negative value showed an improvement in colour vision.

	Rudolph et al. 2013	9/10	Directly applicable		The best evidence came from RHODOS where a sub-population (n=39) were assessed for protan and tritan colour confusion. There was a statistically significant improvement for idebenone compared with placebo for tritan colour contrast at both 12 weeks follow-up (difference between groups: -14.51%; 95% CI: -24.19 to -4.83; p = 0.004) and 24 weeks follow-up (difference between groups: -13.63%; 95% CI: -23.61 to -3.66; p = 0.008). Changes in protan colour contrast were not statistically significant at 24-week follow-up (p=0.239). Supportive evidence came from a post-hoc analysis of the sub-set of data originally assessed in RHODOS (Rudolph et al. 2013). This found a statistically significant difference in favour of idebenone in the change of protan and tritan colour contrast sensitivity, for people with discordant VA between eyes at baseline at both 12 and 24-weeks follow-up. When the data was further analysed by age of patient, the results between treatment groups showed a statistically significant difference in tritan colour contrast for people who were younger than 30 years at baseline at both 12 and 24 weeks. Results suggest idebenone may be effective in improving or preserving colour vision, especially in the subgroups of people with discordant VA, and people younger than 30 years. Results should be interpreted with caution, as these were based on a small sub analysis of people originally completing the RHODOS trial, which means there is uncertainty if results can be generalised to a wider population. RHODOS also had a short follow-up and therefore provides limited evidence on the long-term benefits of idebenone therapy.
Health related quality of life	Klopstock et al. 2011 (RHODOS data reported only in EPAR)	NSF-LTC score not applicable	Directly applicable	Grading not applicable	Quality of life was measured using 2 validated quality of life index questionnaires. The Visual Function Index (VF-14) is a brief (18 questions) self-reported questionnaire designed to measure functional impairment and covers 14 aspects of visual function. The scores are graded using a 0 to 4-point scale and multiplied by 25 to give a value of 0 to 100, where a lower score indicates the person has more difficulty in doing all applicable activities because of their vision. The Clinician's Global Impression of Change (CGIC) is a 3-item observer-rated scale that measures global improvement or change in illness experience. It is rated on a 7-

	RHODOS OFU (data reported only in EPAR)	NSF-LTC score not applicable	Directly applicable		point scale, with the severity of illness scale using a range of responses. Scores range from 1 (very much improved) through to 7 (very much worse). The best evidence came from RHODOS, at 24-weeks follow up, where the change from baseline in VF-14 scores was assessed in a sub-set of patients. There was no difference in change scores between people receiving idebenone or people receiving placebo (estimated mean treatment difference = -1.37; 95%CI = -6.25 to 3.51; P=0.577). Similar findings were reported in the RHODOS-OFU, which found the overall changes recorded during RHODOS and RHODOS-OFU were small and differences between idebenone and placebo groups were not statistically significant, although there was a small worsening in the idebenone group (-1.7%) compared with a small improvement in the placebo group (2.4%; p=0.205) between RHODOS baseline to the RHODOS-OFU. Statistical analyses were not reported for CGIC scores during RHODOS, however, the scores from the idebenone group and placebo group were similar when recorded at 24-weeks follow-up. The EPAR states that these results suggest any potential improvement in vision in patients treated with idebenone did not translate into benefits for the patient's daily activities and health-related quality of life. Although the overall benefit of idebenone to health-related quality of life currently remains unclear, it is important to note that the RHODOS trial included a relatively small, mixed population of people at various stages of their disease progression with a short follow-up and therefore provides limited evidence on the long-term benefits of idebenone therapy.
Safety and tolerability	Klopstock et al. 2011	7/10	Directly applicable	B	Descriptive data on the safety and tolerability of idebenone was collected for all patients in RHODOS and for patient taking part in the EAP (reported in the EPAR). In RHODOS the treatment drug was well tolerated with most adverse events being mild or moderate in intensity. The two serious adverse events reported (1 in the idebenone treatment group and 1 in the placebo group) were considered unrelated to treatment. No deaths were reported in RHODOS. Similar findings were found in the EAP with most adverse events regarded as mild or moderate. The reported serious adverse events were considered unrelated to idebenone treatment. These results suggest idebenone was well-tolerated and considered safe. The EPAR noted the available safety profile for idebenone was considered benign with most AEs being mild or moderate and few reports of serious AEs. However, the
	EAP march 2015 data cut off reported in the EPAR				

					EPAR noted available safety data in the target population were limited. It is important to note that the RHODOS trial included a relatively small, mixed population of people at various stages of their disease progression longer term evidence from the EAP is limited to a small population this therefore provides limited evidence on the long-term benefits of idebenone therapy.

3 Related NICE guidance and NHS England clinical policies

Published

Mitochondrial disorders in children: Co-enzyme Q10 (2017) NICE Evidence Summary 11

4 References

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This clinical evidence review has been written by NICE, following the process set out in the standard operating procedure.

Appendix 1 Search strategy

Databases

Database: Ovid MEDLINE(R) ALL
Platform: Ovid
Version: 1946 to 3rd July 2018
Search date: 5th July 2018
Number of results retrieved: 37
Search strategy:

Database: Ovid MEDLINE(R) ALL <1946 to July 02, 2018>

1 optic atrophy, hereditary, leber/ (854)
2 leber*.tw. (3025)
3 (optic* adj (neuroretinopat* or atroph*)).tw. (3956)
4 LHON.tw. (895)
5 or/1-4 (6742)
6 idebenone.tw. (461)
7 raxone.tw. (4)
8 sovrima.tw. (0)
9 noben.tw. (11)
10 "CV 2619".tw. (28)
11 CV2619.tw. (0)
12 avan.tw. (13)
13 catena.tw. (1439)
14 cerestabon.tw. (0)
15 mnesis.tw. (2)
16 "qsa 10".tw. (5)
17 qsa10.tw. (0)
18 "snt mc17".tw. (1)
19 sntmc17.tw. (0)
20 or/6-19 (1925)
21 5 and 20 (45)
22 Animals/ not (Humans/ and Animals/) (4436891)
23 21 not 22 (42)
24 limit 23 to (comment or congresses or editorial or letter) (5)
25 23 not 24 (37)

Database: Embase
Platform: Ovid
Version: 1974 to July 3rd, 2018
Search date: 5th July 2018
Number of results retrieved: 135
Search strategy:

1 Leber hereditary optic neuropathy/ (1654)
2 leber*.tw. (3777)
3 (optic* adj (neuroretinopat* or atroph*)).tw. (5204)
4 LHON.tw. (1255)
5 or/1-4 (9032)

6 idebenone/ (1352)
7 idebenone.tw. (675)
8 raxone.tw. (32)
9 sovrima.tw. (10)
10 noben.tw. (17)
11 "CV 2619".tw. (80)
12 CV2619.tw. (0)
13 avan.tw. (44)
14 catena.tw. (247)
15 cerestabon.tw. (2)
16 mnesis.tw. (18)
17 "qsa 10".tw. (3)
18 qsa10.tw. (0)
19 "snt mc17".tw. (10)
20 sntmc17.tw. (0)
21 or/6-20 (1631)
22 5 and 21 (208)
23 nonhuman/ not (human/ and nonhuman/) (4185856)
24 22 not 23 (201)
25 limit 24 to (conference abstract or conference paper or "conference review" or editorial or letter) (66)
26 24 not 25 (135)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED
Platform: Wiley
Version:
CDSR – 7 of 12, July 2018
DARE – 2 of 4, April 2015 (legacy database)
CENTRAL – 6 of 12, June 2018
HTA – 4 of 4, October 2016
NHS EED – 2 of 4, April 2015 (legacy database)
Search date: 4th July 2018
Number of results retrieved: CDSR – 0; DARE – 0; CENTRAL – 4; HTA – 0; NHS EED – 3.
Search strategy:

#1 [mh ^"optic atrophy, hereditary, leber"]
#2 leber*: ti, ab
#3 (optic* near/1 (neuroretinopat* or atroph*)): ti, ab
#4 LHON: ti, ab
#5 {or #1-#4}
#6 idebenone: ti, ab
#7 raxone: ti, ab
#8 sovrima: ti, ab
#9 noben: ti, ab
#10 "CV 2619": ti, ab
#11 CV2619: ti, ab
#12 avan: ti, ab
#13 catena: ti, ab
#14 cerestabon: ti, ab
#15 mnesis: ti, ab
#16 "qsa 10": ti, ab
#17 qsa10: ti, ab

#18 "snt mc17": ti, ab
#19 sntmc17: ti, ab
#20 {or #6-#19}
#21 #5 and #20
#22 conference:pt
#23 "clinicaltrials.gov":so
#24 #21 not (#22 or #23)

Trials registries

Clinicaltrials.gov

Search date: 5th July 2018
Number of results retrieved: 5
Search strategy and link to results page:

Condititon: Leber OR Lebers OR optic OR optical OR LHON

Other terms: idebenone OR raxone OR sovrima OR noben OR (CV 2619) OR CV2619 OR avan OR catena OR cerestabon OR (qsa 10) OR qsa10 OR (snt mc17) OR sntmc17

Clinicaltrialsregister.eu

Search date: 5th July 2018
Number of results retrieved: 4 (3 duplicates of studies registered in clinicaltrials.gov)
Search strategy and link to results page:

(Leber OR Lebers OR optic OR optical OR LHON) AND (idebenone OR raxone OR sovrima OR noben OR (CV 2619) OR CV2619 OR avan OR catena OR cerestabon OR (qsa 10) OR qsa10 OR (snt mc17) OR sntmc17)

Excluded results from trials registry searches

Study title	Reason discarded
RHODOS Follow-up Single-visit Study	Study withdrawn
ORAL TAC 101 AS SECOND LINE TREATMENT IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA WHO RECEIVED SO...	Different indication

Appendix 2 Study selection

The search strategy presented in appendix 1 yielded 144 studies. These were screened on titles and abstracts in EPPI Reviewer according to the following inclusion/exclusion criteria:

Sifting criteria	**Inclusion**	**Exclusion**
Population	Adults and adolescents with LHON	Non-humans/ healthy volunteers
Intervention	Idebenone (Raxone)	
Comparator	Best supportive care	
Outcomes	**Visual acuity, including:** • Best recovery of visual acuity (visual clarity) in either right or left eye (or both eyes) • Change in visual acuity in either right or left eye (or both eyes) • Clinically relevant recovery of visual acuity in either right or left eye (or both eyes) • Clinically relevant stabilisation of visual acuity in either right or left eye (or both eyes) • Number of eyes/patients showing improved visual acuity **Visual field assessment, including:** • Change in scotoma area • **Visual function/ structural assessment, including:** • Change in colour-contrast sensitivity • Change in retinal nerve fibre layer **Other** • Patient reported outcomes	

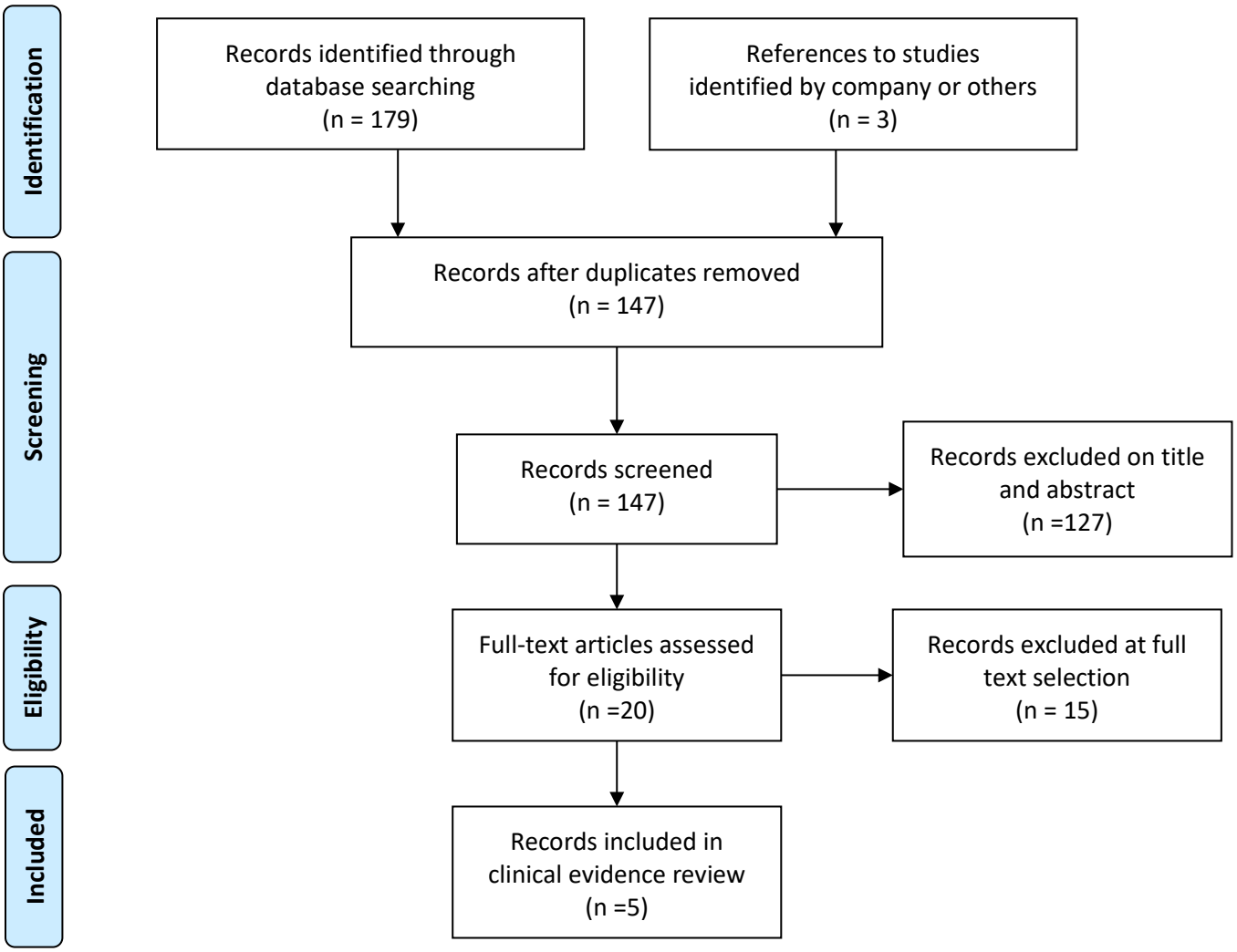
	• Use of assistive devices	
Other		Abstracts Non-English language Duplicates Opinion pieces, commentaries, /editorials/ letters,

Table 4 Studies excluded at full text

Study reference	Reason for exclusion
Anonymous: (2011) Idebenone (Catena) for leber's hereditary optic neuropathy - first line (Structured abstract). Health Technology Assessment Database (4),	Bibliographic reference only
Barnils N, Mesa E, Munoz S, Ferrer-Artola A, and Arruga J (2007) [Response to idebenone and multivitamin therapy in Leber's hereditary optic neuropathy]. Respuesta a la idebenona asociada a multivitaminoterapia en neuropatia optica hereditaria de Leber. 82(6), 377-80	Case study/ series: Details reported in EPAR
Barreda Gago, D, Gomez Ledesma, I, Santiago Rodriguez, M D L. A, Hernandez Galilea, and E (2016) Leber's hereditary optic neuropathy with G11778A mutation in mitochondrial DNA. Management of a case. Revista Mexicana de Oftalmologia 90(6), 295-299	Case study/ series
Carelli V, Barboni P, Zacchini A, Mancini R, Monari L, Cevoli S, Liguori R, Sensi M, Lugaresi E, and Montagna P (1998) Leber's Hereditary Optic Neuropathy (LHON) with 14484/ND6 mutation in a North African patient. Journal of the neurological sciences 160(2), 183-8	Case study/ series: Details reported in EPAR
Chen J, Ren M W, and Du Y (2018) Ineffectiveness of low-dosage idebenone on chinese patients with leber's hereditary optic neuropathy: Report of two cases. Kuwait Medical Journal 50(1), 95-99	Case study/ series: Did not receive licensed dose
Cheng S W, Ko C H, Yau S K, Mak Chloe, Yuen Y F, and Lee C Y (2014) Novel use of idebenone in Leber's hereditary optic neuropathy in Hong Kong. Hong Kong medical journal = Xianggang yi xue za zhi 20(5), 451-4	Case study/ series
Cortelli P, Montagna P, Pierangeli G, Lodi R, Barboni P, Liguori R, Carelli V, Iotti S, Zaniol P, Lugaresi E, and Barbiroli B (1997) Clinical and brain bioenergetics improvement with idebenone in a patient with Leber's hereditary optic neuropathy: a clinical and 31P-MRS study. Journal of the neurological sciences 148(1), 25-31	In vivo/ in vitro data only
Isashiki Y, Ohba N, and Uto M (1993) Systemic administration of idebenone to the optic atrophic stage of Leber's hereditary optic neuropathy. Neuro-Ophthalmology Japan 10(2), 163-167	Article not in English

Klopstock T, Metz G, Yu-Wai-Man P, Büchner B, Gallenmüller C, Bailie M, Nwali N, Griffiths Pg, Livonius B, Reznicek L, Rouleau J, Coppard N, Meier T, and Chinnery Pf (2013) Persistence of the treatment effect of idebenone in Leber's hereditary optic neuropathy. Brain 136(Pt 2), e230	Letter/ Commentary: Details reported in EPAR
Jorstad Oystein Kalsnes, Odegaard Eva Meling, Heimdal Ketil Riddervold, Kerty Emilia, Heimdal Ketil Riddervold, and Kerty Emilia (2018) Leber Hereditary Optic Neuropathy Caused by a Mitochondrial DNA 10663T>C Point Mutation and Its Response to Idebenone Treatment. Journal of neuro-ophthalmology: the official journal of the North American Neuro-Ophthalmology Society 38(1), 129-131	Article not available
Mashima Y, Kigasawa K, Wakakura M, and Oguchi Y (2000) Do idebenone and vitamin therapy shorten the time to achieve visual recovery in Leber hereditary optic neuropathy? Journal of neuro-ophthalmology: the official journal of the North American Neuro-Ophthalmology Society 20(3), 166-70	Case study/ series: Details reported in EPAR
Mashima Y, Sato E A, and Oguchi Y (2001) Detection of fenestrated central scotoma by scanning laser ophthalmoscope microperimetry in a patient with Leber's hereditary optic neuropathy after visual recovery. Neuro-Ophthalmology 25(3), 115-121	Case study/ series
Newman N J (2011) Treatment of Leber hereditary optic neuropathy. Brain 134(9), 2447-2450	Letter/ Commentary
Sabet-Peyman Esfandiar J, Khaderi Khizer R, and Sadun Alfredo A (2012) Is Leber hereditary optic neuropathy treatable? Encouraging results with idebenone in both prospective and retrospective trials and an illustrative case. Journal of neuro-ophthalmology: the official journal of the North American Neuro-Ophthalmology Society 32(1), 54-7	Case study/ series: Details reported in EPAR

Figure 1 Flow chart of included studies



Appendix 3 Evidence tables

Table 5 Klopstock et al. 2011 (RHODOS trial)

Study reference	Klopstock T, Yu-Wai-Man P, Dimitriadis K, Rouleau J, Heck S, Bailie M et al. (2011) A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy. Brain, 134: 2677-2686
Unique identifier	Rescue of Hereditary Optic Disease Outpatient Study (RHODOS) NCT00747487
Study type (and NSF-LTC study code)	Prospective randomised double-blind placebo-controlled trial phase II (P1)
Aim of the study	To consider the therapeutic effects of idebenone in LHON patients in a randomised controlled trial
Study dates	Nov 2007 to Feb 2010 (NB only reported in the clinical trials register and not reported in published paper)
Setting	Multi centre 3 sites (Germany, England, Canada)
Number of participants	N=85 Idebenone (n=55) placebo (n=30) NB: Meets 80% statistical power: To achieve power calculations a total of 84 participants were necessary
Population	People aged 14 to 65 years with LHON
Inclusion criteria	People between 14 and 64 years of age. m.3460G>A, m.11778G>A, or m.14484T>C mitochondrial DNA mutations. Had experienced vision loss due to LHON in previous 5 years. Did not take drugs of abuse and were not pregnant nor breastfeeding. No explanation for the visual failure besides LHON[a] Body weight ≥45 kg[a] Negative urine pregnancy test at Screening and at Baseline (women of childbearing potential) [a]
Exclusion criteria[a]	Treatment with Coenzyme Q10 or idebenone within 1 month prior to Baseline. Pregnancy and/or breast-feeding. Weekly alcohol intake 35 units (men) or 24 units (women). Current drug abuse. Clinically significant abnormalities of clinical haematology or biochemistry including, but not limited to, elevations > 2 x upper limit of normal of aspartate aminotransferase (AST), alanine aminotransferase (ALT) or creatinine. Participation in another clinical trial of any investigational drug within 3 months prior to Baseline. Other factor that, in the investigator's opinion, excluded the patient from entering the study.
Intervention(s)	900mg per day (300 mg 3 times a day)
Comparator(s)	placebo

Length of follow-up	24 weeks
Outcomes	Primary outcome: • Best recovery (least worsening) of visual acuity between baseline and 24 weeks (best recovery of logMAR)
	Secondary outcomes: • Change from baseline in best visual acuity (best logMAR) • Change from baseline in visual acuity of best eye • Change from baseline in visual acuity for both eyes • Responder analysis (involving counting of patients and eyes that changed) • Change from baseline in retinal nerve fibre layer thickness • Change from baseline in colour contrast sensitivity • Clinical Global Impression of Change (CGIC) • Change in VF-14 score (Health related quality of life)[a] • Change in self-reported general energy levels assessed by Visual Analog Scale (VAS) from baseline to Week 24[a] •
	Safety outcomes: • Number of adverse events • Number of serious adverse events • Changes in vital signs
Source of funding	• Santhera pharmaceuticals
[a]details reported in EPAR only and not in published article	

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	1/2	Partly: Clearly defined as first RCT in this study group but aim is not specifically defined. It is simply described as – to explore the therapeutic effects of idebenone in LHON rather than providing any specific efficacy or safety requirements
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Yes, double blind RCT
3. Are the methods clearly described?	1/2	Partly: Inclusion criteria reported but no detailed exclusion criteria. Although clear reporting of randomisation and masking, there is limited detail of the treatment procedure
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	Partly, recognises limitations given new treatment and technology advances in assessment methods but would have liked to see full data on safety as only narrative interpretation provided
5. Are the results generalisable?	2/2	Yes
Total	7/10	
Applicability *	Directly / indirectly applicable	Directly applicable

* Note - Direct studies focus on people with the indication and characteristics of interest.
Indirect studies are based on evidence extrapolated from populations with other conditions and characteristics.
We'll put this in our methods manual

Table 6 Rudolph et al. (2013)

Study reference	Rudolph R, Dimitriadis K, Büchner B, Heck S et al. Effects of idebenone on color vision in patients with leber hereditary optic neuropathy, 2012. Journal of Neuropthalmology, 0;1-7
Unique identifier	Effects of idebenone on color vision in patients with Leber Hereditary Optic Neuropathy
Study type (and NSF-LTC study code)	Post-hoc sub-analysis of 39 people completing the RHODOS trial (S2)
Aim of the study	To investigate the red–green (protan) and blue–yellow (tritan) colour contrast sensitivity, in a subgroup of LHON patients enrolled in the RHODOS study and to describe the therapeutic benefit of idebenone treatment on colour vision
Study dates	As reported in RHODOS trial
Setting	One site participating in RHODOS trial
Number of participants	N= 39 patients included in efficacy population out of 111 eligible (patients not included in efficacy population had vision loss onset > 12 months)
Population	People carrying 1 of the 3 major LHON mtDNA mutations and vision loss caused by LHON within 5 years before study enrolment
Inclusion criteria	People of any age with confirmed diagnosis of LHON. Patients were stratified by disease history (onset ≤1 year or >1 year) and mtDNA mutation
Exclusion criteria	Not reported
Intervention(s)	Idebenone 900mg per day (300 mg 3 times a day)
Comparator(s)	placebo
Length of follow-up	24 weeks
Outcomes	Primary outcome • Colour contrast sensitivity at baseline
	Secondary outcomes • Efficacy of idebenone on colour vision in LHON patients • Change in protan colour contrast sensitivity • Change in tritan colour contrast sensitivity
	Safety outcomes • Number of adverse events • Number of serious adverse events • Number of discontinuations to adverse events

Source of funding	• Santhera pharmaceuticals

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	Yes, full clear research aims. Presenting several objectives of relevance
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Post-hoc analysis of sub-group originally assessed for colour contrast-sensitivity
3. Are the methods clearly described?	1/2	Reports minimum details about original methodology. Reverting back to original study records for further detail and limited details on analysis approach
4. Are the data adequate to support the authors' interpretations / conclusions?	2/2	Yes, full clear reporting, explores uncertainty by considering sub-populations
5. Are the results generalisable?	2/2	Yes
Total	9/10	
Applicability *	Directly / indirectly applicable	

* Note - Direct studies focus on people with the indication and characteristics of interest.
Indirect studies are based on evidence extrapolated from populations with other conditions and characteristics.
We'll put this in our methods manual

Appendix 4 Results tables

Table 7 Klopstock, 2011 (RHODOS)

	Idebenone	Placebo
Primary outcome: Intention to treat (ITT) population		
Visual acuity – best recovery/least worsening mean difference (95% confidence interval)		
	N=53	**N=29**
Best recovery (least worsening) of visual acuity (change of logMAR between baseline and 24-week end-point)	-0.135 (-0.216 to -0.054) (+6 letters[a])	-0.071 (-0.176 to 0.034) (+3 letters[a])
LogMAR difference between groups at 24 weeks	-0.064 (95% CI: -0.184 to 0.055; P = 0.291) (3 letters[a])	
LogMAR difference between groups at 24 weeks (combined patients carrying m.11778G4A and m.3460G4A mutation)	-0.092 (-0.229 to 0.045; P = 0.187)	
Correlation between observed changes and patients Clinical Global Impression of Change	R = -0.32, P = 0.005	
LogMAR estimated mean difference between groups at 24 weeks (sub analysis of patients with concordant visual acuity at baseline)	+ 0.056 (-0.091 to + 0.202; P = 0.452)	
LogMAR estimated mean difference between groups at 24 weeks (sub analysis of patients with discordant visual acuity at baseline – LogMAR	-0.285 (- 0.502 to - 0.068; P = 0.011)	

difference >0.2 between eyes)		
Secondary outcome: Intention to treat ITT population		
Visual acuity - Best VA mean difference (95% confidence intervals)		
	N=53	**N=29**
Change from baseline in best visual acuity (change of logMAR between baseline and 24-week end-point)	-0.035 -0.126, 0.055) (+1 letter)	+0.085 (-0.032, 0.203) (-4 letters)
LogMAR difference between groups at 24 weeks	-0.120 (-0.2546, 0.0137; P=0.078) (6 letters)	
LogMAR difference between groups at 24 weeks (combined patients carrying m.11778G4A and m.3460G4A mutation)	-0.169 (-0.326 to -0.011; P = 0.037)	
Correlation between observed changes and patients Clinical Global Impression of Change	R = -0.34, P = 0.002	
LogMAR estimated mean difference between groups at 24 weeks (post hoc sub analysis of patients with concordant visual acuity at baseline)	+ 0.037 (95% CI: -0.107 to + 0.180; P = 0.613)	
LogMAR estimated mean difference between groups at 24 weeks (sub analysis of patients with discordant visual acuity at baseline – LogMAR difference >0.2 between eyes)	-0.421 (-0.692 to -0.150; P = 0.003)	
Visual acuity – Best eye mean difference (95% confidence interval)		

Change from baseline in visual acuity of best eye (change of logMAR between baseline and 24-week end-point)	-0.030 (-0.120 to 0.060 (letters not reported)	+ 0.098 (-0.020 to 0.215) (letters not reported)
LogMAR difference between groups at 24 weeks	-0.128 (-0.262 to 0.006; P = 0.061)	
Correlation between observed changes and patients Clinical Global Impression of Change	R = -0.33, P = 0.004	
LogMAR estimated mean difference between groups at 24 weeks (post hoc sub analysis of patients with concordant visual acuity at baseline)	0.022 (-0.120 to + 0.165; P = 0.757)	
LogMAR estimated mean difference between groups at 24 weeks (post hoc sub analysis of patients with discordant visual acuity at baseline – LogMAR difference >0.2 between eyes)	-0.415 (-0.686 to -0.144; P = 0.003)	
Visual acuity- all eyes mean difference (95% confidence interval)		
Change from baseline in visual acuity of both eyes (change of logMAR between baseline and 24-week end-point)	-0.054 (-0.114 to 0.005)	+ 0.046 (-0.032 to 0.123)
LogMAR difference between groups at 24 weeks	-0.100 (- 0.188 to -0.012; P = 0.026)	
Correlation between observed changes and patients Clinical	R = -0.32, P<0.001	

Global Impression of Change			
LogMAR estimated mean difference between groups at 24 weeks (post hoc sub analysis of patients with concordant visual acuity at baseline)	+ 0.028 (-0.070 to + 0.125; P = 0.577)		
LogMAR estimated mean difference between groups at 24 weeks (post hoc sub analysis of patients with discordant visual acuity at baseline – LogMAR difference >0.2 between eyes)	-0.348 (-0.519 to -0.176; P = 0.0001)		
Responder analysis for change in visual acuity Intention to treat (ITT) population Proportion of patients with change of logMAR of 0.2 or more at Week 24			
N=82	**Idebenone N / n (%)**	**Placebo N / n (%)**	**P value**
Improvement: best recovery in visual acuity	20/53 (37.7%)	7/29 (24.1%)	P=0.231
Improvement: best visual acuity	14/53 (26.4%)	5/29 (17.2%)	P=0.420
Improvement: visual acuity of all eyes	30/106 eyes (28.3%)	10/58 eyes (17.2%)	P=0.131
Worsening in visual acuity of all eyes	18/106 (17.0%)	17/58 (29.3%)	P=0.075
Responder analysis for change in visual acuity Intention to treat (ITT) population: Proportion of patients with change of logMAR of 0.2 or more at Week 24 Subgroup of patients with discordant visual acuities at baseline (n = 30) (%)			
N=30	**Idebenone N / n (%)**	**Placebo N / n (%)**	**P value**
Improvement: best recovery in visual acuity	11/20 (55.0%)	1/10 (10.0%)	P=0.024
Improvement: best visual acuity	6/20 (30.0%)	0/10 (0.0%)	P=0.074
Improvement: in visual acuity of all eyes	15/40 (37.5\5)	1/20 (5.0%)	P=0.011
Worsening in visual acuity of all eyes	8/40 (20.0%)	9/20 (45.0%)	P=0.067
Responder analysis for change in visual acuity Intention to treat (ITT) population:			

Proportion of patients with logMAR ≤0.5 (best corrected vision) in at least one eye at baseline			
N=8	**Idebenone N / n (%)**	**Placebo N / n (%)**	**P value**
Deteriorate to logMAR 1.0 or more (legal blindness)	0/6 (0%)	2/2 (100%)	P=0.036
Responder analysis for change in visual acuity: Intention to treat (ITT) population: Subgroup of patients/ eyes that were off chart at baseline			
N=38	**Idebenone N / n (%)**	**Placebo N / n (%)**	**P value**
Could read at least five letters on the chart at Week 24 with at least one eye	7/25 (28.0%)	0/13 (0.0%)	P=0.072
Eyes that were off chart at baseline: Could read at least five letters on the chart at Week 24	12/61 (19.7%)	0/29 (0.0%)	P=0.008
Responder analysis: Proportion of Patients with CRR from Baseline at Week 24 modified ITT (mITT) population[a]:			
N=81	**Idebenone N=53 N (%)**	**Placebo N=28 N (%)**	**P value**
Proportion of patients with VA recovery from baseline (change of logMAR ≥ 0.2 if 'on chart' or logMAR ≥1.6 if 'off chart' at baseline)	16 (30.2%)	2 (7.1%)	P=0.0234
Proportion of eyes with VA recovery from baseline (change of logMAR ≥ 0.2 if 'on chart' or logMAR ≥1.6 if 'off chart' at baseline)	21 eyes (19.8%)	2 eyes (3.6%)	P=0.0041
Proportion of patients with CRR from the VA nadir (lowest reported VA)	18 (34.0%)	3 (5.4%) %)	P=0.0321
Proportion of patients with CRR from the VA nadir (lowest reported VA) in <1-year disease duration	5 (26.3%)	1 (11.1%)	P=0.6296

Proportion of patients with CRR from the VA nadir (lowest reported VA) in ≥ 5years disease duration	13 (38.2%)	2 (10.5%)	P=0.0545
Proportion of patients with clinically relevant worsening (CRW) from baseline (change from logMAR ≤1.6 to "off-chart" or a change of logMAR 0.2 "on-chart")	2 (3.8%)	2 (7.1%)	P=0.6508
	Idebenone	**Placebo**	
N=82	**N=53**	**N=28**	
Primary outcome: modified intention to treat (mITT) population[a] mean difference (95% confidence interval)			
Visual acuity – best recovery/least worsening			
Best recovery (least worsening) of visual acuity (change of logMAR between baseline and 24-week end-point)	-0.136 (-0.212, -0.060) (+6 letters)	-0.036 (-0.137, -0.065) (+1 letters)	
LogMAR difference between groups at 24 weeks	-0.100 ± 0.058 (-0.214, -0.01; P=0.0862) (5 letters)		
Secondary outcome: modified intention to treat (mITT) population[a] mean difference (95% confidence interval)			
	Idebenone	**Placebo**	
	N=53	**N=28**	
Visual acuity – Best VA			
Best visual acuity (change of logMAR between baseline and 24-week end-point)	-0.037 (-0.123, 0.049) (+1 letter)	0.123 (0.010, 0.237) (-6 letters)	
LogMAR difference between groups at 24 weeks	-0.160 ± 0.065 (-0.289, -0.031; P=0.015) (8 letters)		
Primary outcome: modified intention to treat (mITT) population[a] mean difference (95% confidence interval) sub analysis in people with G11778A mutation			
	Idebenone	**Placebo**	
	N=35	**N=18**	

Visual acuity – best recovery/least worsening		
Best recovery (least worsening) of visual acuity (change of logMAR between baseline and 24-week end-point)	-0.139 (-0.225, -0.053) (letter change not reported)	0.009 (-0.111, 0.129) (letter change not reported)
LogMAR difference between groups at 24 weeks	-0.148 (standard error 0.073; P=0.047 (difference in letters not reported)	
Primary outcome: modified intention to treat (mITT) population[a] **mean difference (95% confidence interval) sub analysis in people with < 1-year disease onset**		
	Idebenone	**Placebo**
	N=19	**N=9**
Visual acuity – best recovery/ least worsening		
Best recovery (least worsening) of visual acuity (change of logMAR between baseline and 24-week end-point)	-0.093 (-0.213, 0.027) (letter change not reported)	0.060 (-0.114, 0.234) (letter change not reported)
LogMAR difference between groups at 24 weeks	-0.154 (standard error 0.096; P=0.116 (difference in letters not reported)	
Secondary outcome: modified intention to treat (mITT) population[a] **mean difference (95% confidence interval) sub analysis in people with G11778A mutation**		
	Idebenone	**Placebo**
	N=35	**N=18**
Visual acuity – Best VA		
Best visual acuity (change of logMAR between baseline and 24-week end-point)	-0.045 (-0.141, 0.052) (letter change not reported)	0.153 (0.018, 0.288) (letter change not reported)
LogMAR difference between groups at 24 weeks	-0.198 (standard error 0.083; P=0.019 (difference in letters not reported)	
Secondary outcome: modified intention to treat (mITT) population[a] **mean difference (95% confidence interval) sub analysis in people with < 1-year disease onset**		
	Idebenone	**Placebo**
	N=19	**N=9**
Visual acuity – Best VA		

Best visual acuity (change of logMAR between baseline and 24-week end-point)	0.051 (-0.124, 0.227) (letter change not reported)	0.394 (0.144, 0.643) (letter change not reported)
LogMAR difference between groups at 24 weeks	-0.342 (standard error 0.137; P=0.016) (difference in letters not reported)	
	Idebenone	**Placebo**
N=39	**N=28**	**N=11**
Secondary outcome: Change in colour contrast sensitivity[b] (% change)		
Change from baseline in colour contrast sensitivity for red-green (protan) at 24 weeks[c]	Idebenone = +1.4% (worsening); placebo = +5.3% (worsening) Difference between groups = -3.9% (superiority idebenone) numerical statistical estimates or CIs not reported; (p=0.239)	
Change from baseline in colour contrast sensitivity for blue-yellow (tritan) at 24 weeks[c]	Idebenone = -7.2% (improvement) placebo (+6.4%) worsening Difference between groups = -13.63 % (-23.61 to -3.66; p=0.008; (superiority idebenone)	
Secondary outcome: Retinal nerve fibre layer thickness		
Pattern of retinal nerve fibre layer thickness patients grouped by disease onset of ≤6 months, 6 months to 1 year, and >1 year	No difference in the pattern of retinal nerve fibre layer thickness at baseline. There was a trend towards maintaining retinal nerve fibre layer thickness in the idebenone group in superior, nasal and inferior quadrants, among patients with ≤6 month's disease history however, no formal statistical analysis was carried out, due to small sample size.	
Secondary outcome: Change in health-related quality of life		
Change in VF-14 score at 24 weeks[a]	Estimated mean treatment difference[a] -1.37 (-6.25, 3.51; p=0.577).	
Change in Clinician's Global Impression of Change (CGIC) score at 24 weeks[a]	12 (22.6%) idebenone; 7 (24.1%) placebo reported improvement 43 (81.1%) idebenone; 24 (82.8%) placebo reported less fatigue/ no change in fatigue levels	
Secondary outcome: Change in VAS score (general energy levels) at 24 weeks		
Change in self-reported general energy levels assessed by Visual Analog Scale (VAS) from baseline to Week 24[a]	Idebenone = 0.37 mm; placebo = 2.17 mm Estimated mean treatment difference = - 1.80; (1.37, 7.77; p=0.709)	
Secondary outcome: Safety and tolerability		

Mean pill count compliance = 96.5%, (SD 6.8%). Premature discontinuations n=7 (n = 4/30 for placebo; n = 3/55 for idebenone) Discontinuation due to adverse events n=2 (n=1/30 for placebo; n=1/55 for idebenone) Serious adverse events n=2 (placebo group = n=1; epistaxis; idebenone group n=1 infected epidermal cyst. Both cases were not considered to be due to the study medication. No clinically significant changes of vital signs and other biochemical or haematological parameters were observed
[a] Data reported only in EPAR [b] Colour contrast sensitivity test performed on subset of patients in one of the study centres [c] Results based on both eyes combined [d] Reported values for mITT are the same as those reported in ITT

Table 8 Rudolph, 2013

Primary outcome: Colour contrast sensitivity at baseline-mean (SD)			
Proportion of patients with colour contrast confusion at baseline	82.6% (32.6) = protan 80.15% (34.6) = tritan		
Number of eyes with normal colour contrast sensitivity at baseline[a] n (%)	2 (2.6%) = protan 5 (6.4%) = tritan		
Efficacy of idebenone on colour vision mean (standard error)			
	Idebenone	**Placebo**	**P value**
Mean change from baseline in protan colour contrast sensitivity (all patients)	0.2 (3.1) at 12 weeks 1.4 (3.1) at 24 weeks	6.3 (3.8) at 12 weeks 5.3(3.9) at 24 weeks	Estimated difference between groups = -6.1 (3.2) p=0.057 at 12 weeks Estimated difference between groups = -3.9 (3.3) p=0.239 at 24 weeks
Mean change from baseline in tritan colour contrast sensitivity (all patients)	-8.3 (4.7) at 12 weeks -7.3 (4.7) at 24 weeks	6.2 (5.9) at 12 weeks 6.4 (6.0) at 24 weeks	Estimated difference between groups = -14.5 (4.9) p=0.004 at 12 weeks Estimated difference between groups = -13.6 (5.0) p=0.008 at 24 weeks
Mean change from baseline in protan colour contrast sensitivity (patients	2.8 (5.0) at 12 weeks 1.6 (5.0) at 24 weeks	19.4 (6.3) at 12 weeks 15.1 (6.6) at 24 weeks	Estimated difference between groups = -16.6 (7.1) p=0.022 at 12 weeks

with discordant VA at baseline)			Estimated difference between groups = -13.5 (7.2) p=0.067 at 24 weeks
Mean change from baseline in tritan colour contrast sensitivity (patients with discordant VA at baseline)	0.5 (4.3) at 12 weeks -4.2 (4.3) at 24 weeks	13.3 (5.8) at 12 weeks 16.3 (6.4) at 24 weeks	Estimated difference between groups = -12.7 (6.6) p=0.060 at 12 weeks Estimated difference between groups = -20.4 (6.9) p=0.005 at 24 weeks
Mean change from baseline in protan colour contrast sensitivity (patients ≤30 years at baseline)	0.8 (2.6) at 12 weeks 2.5 (2.6) at 24 weeks	4.2 (3.4) at 12 weeks 5.3 (3.5) at 24 weeks	Estimated difference between groups = -3.4 (4.0) p=0.400 at 12 weeks Estimated difference between groups = -2.8 (4.1) p=0.486 at 24 weeks
Mean change from baseline in tritan colour contrast sensitivity (patients ≤30 years at baseline)	-12.9 (4.2) at 12 weeks -10.8 (4.2) at 24 weeks	6.3 (5.6) at 12 weeks 6.8 (5.8) at 24 weeks	Estimated difference between groups = -19.2 (6.6) p=0.005 at 12 weeks Estimated difference between groups = -17.6 (6.7) p=0.010 at 24 weeks
Mean change from baseline in protan colour contrast sensitivity (patients >30 years at baseline)	3.6 (3.7) at 12 weeks 4.1 (3.7) at 24 weeks	18.9 (5.5) at 12 weeks 8.5 (7.3) at 24 weeks	Estimated difference = -15.3 (6.9) p=0.032 at 12 weeks Estimated difference = -4.4 (7.6) p=0.5.65 at 24 weeks
Mean change from baseline in tritan colour contrast sensitivity (patients >30 years at baseline)	1.1 (1.8) at 12 weeks 0.5 (1.8) at 24 weeks	5.3 (2.5) at 12 weeks 2.6 (3.0) at 24 weeks	Estimated difference between groups = -4.2 (3.2) p=0.197 at 12 weeks Estimated difference between groups = -2.1 (3.4) p=0.537 at 24 weeks
Mean change from baseline in protan colour contrast sensitivity (patients ≤1-year diagnosis at baseline)	5.5 (4.3) at 12 weeks 9.3 (4.3) at 24 weeks	11.8 (5.8) at 12 weeks 7.2 (6.7) at 24 weeks	Estimated difference between groups = -6.3 (6.8) p=0.356 at 12 weeks Estimated difference between groups = 2.0

			(7.5) p=0.785 at 24 weeks
Mean change from baseline in tritan colour contrast sensitivity (patients ≤1-year diagnosis at baseline)	-15.7 (7.3) at 12 weeks -7.7 (7.3) at 24 weeks	0.6 (10.0) at 12 weeks 2.5 (11.1) at 24 weeks	Estimated difference between groups = -16.4 (11.7) p=0.170 at 12 weeks Estimated difference between groups = -10.2 (12.6) p=0.423 at 24 weeks
Mean change from baseline in protan colour contrast sensitivity (patients >1-year diagnosis at baseline)	-2.1 (2.1) at 12 weeks -2.5 (2.1) at 24 weeks	-0.8 (3.0) at 12 weeks 0.9 (3.0) at 24 weeks	Estimated difference between groups = -1.3 (2.8) p=0.655 at 12 weeks Estimated difference = -3.3 (2.8) p=0.242 at 24 weeks
Mean change from baseline in tritan colour contrast sensitivity (patients >1-year diagnosis at baseline)	-2.2 (2.7) at 12 weeks -5.3 (2.7) at 24 weeks	6.2 (3.9) at 12 weeks 6.2 (3.9) at 24 weeks	Estimated difference between groups = -8.5 (3.7) p=0.026 at 12 weeks Estimated difference between groups = -11.6 (3.7) p=0.003 at 24 weeks
[a] Defined as ≤6% colour confusion for protan and ≤8% for tritan. LHON, Leber hereditary optic neuropathy.			

Table 9 Data reported only in EPAR

Primary outcome: Data extracted from EAP (clinical cut-off March 2015)	
Proportion of patients with CRR in VA from nadir	24/48 patients (50%) had a CRR 13/24 (54.2%) had a CRR in both eyes 37/96 eyes (38.5%) had a CRR by time of last VA assessment (at time of initial report submitted to the EMA) 34/69 patients (49.3%) had a CRR 55/138 eyes (39.9%) had a CRR by time of last VA assessment (at time of updated report submitted to EMA – clinical cut off 20th March 2015)
Secondary outcome: Data extracted from EAP	
Proportion of patients with CRR by mutation	G11778A mutation = (31.0%) G3460A mutation = (70.0%)

	T14484C mutation = 88.9%)
Time to initial CRR	Mean treatment time from baseline to first CRR was 6.6 months (range 2.5-19.9 months) Mean overall treatment time in patients with CRR at last observation was 11.6 months.
Primary outcome: Data extracted from case record survey (people receiving idebenone treatment)	
Proportion of patients with CRR of VA from nadir	24/48 patients (50%) had a CRR 38/96 eyes (39.6%)
Mean time to onset of CRR	In patients with a CRR, mean time to onset was 16.2 months (range 1.9 to 39.4 months)
Mean magnitude of best CRR (best recovering eye in each patient)	Magnitude = 38 letters (range 8 to 82 letters) 14/39 patients (35.9%) with on-chart vision at presentation 29/ 71 eyes (40.8%) n had no CRW in the VA of at least one eye.
Primary outcome (People without idebenone treatment)	
sCRR in VA from nadir	23/74 patients (31.1%) observed sCRR in at least one eye 36/148 eyes (24.4%) observed sCRR 13/23 patients observed a sCRR in both eyes
Proportions of sCRR by mtDNA mutation	G3460A = 6/12 patients (50.0%) T14484C= 3/7 patients (42.9%) G11778A mutation =14/55 patients (25.5%)
Mean time from disease onset to sCRR	9.9 months (1.0 to 27.5 months)
Magnitude of the best sCRR	Magnitude observed for either eye mean = 39 letters (range 5 to 90 letters)
Abbreviations: EAP; Expanded access programme; CRR clinically relevant recovery; CRW clinically relevant worsening; sCRR spontaneous clinically relevant worsening; mtDNA mitochondrial DNA	

Appendix 5 Grading of the evidence base

NHS England has requested that NICE use the following system for grading the evidence. Each study is assigned one of the following codes:

NSF-LTC Categories of research design

Primary research-based evidence
P1 Primary research using quantitative approaches
P2 Primary research using qualitative approaches
P3 Primary research using mixed approaches (quantitative and qualitative)
Secondary research-based evidence
S1 Meta-analysis of existing data analysis
S2 Secondary analysis of existing data
Review based evidence
R1 Systematic reviews of existing research

For each key outcome, studies were grouped, and the following criteria were applied to achieve an overall grade of evidence by outcome.

Grade	**Criteria**
Grade A	More than 1 study of at least 7/10 quality and at least 1 study directly applicable
Grade B	One study of at least 7/10 which is directly applicable OR More than one study of a least 7/10 which are indirectly applicable OR More than one study 4-6/10 and at least one is directly applicable OR One study 4-6/10 which is directly applicable and one study of least 7/10 which is indirectly applicable
Grade C	One study of 4-6/10 and directly applicable OR Studies 2-3/10 quality OR Studies of indirect applicability and no more than one study is 7/10 quality

Applicability should be classified as:

- Direct studies that focus on people with the indication and characteristics of interest.
- Indirect studies based on evidence extrapolated from populations with other conditions and characteristics.