Summary form

National Institute for Health and Care Excellence

Highly Specialised Technologies Evaluation

Lenadogene nolparvovec for treating Leber's hereditary optic neuropathy caused by the G11778A ND4 mitochondrial mutation [ID1410]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Wording	GenSight Biologics SA	Yes	Thank you for your comment. No action required.
	Leber's Hereditary Optic Neuropathy Society	Yes	Thank you for your comment. No action required.
	United Kingdom Neuro-Ophthalmology Society	No additions or alterations to add.	Thank you for your comment. No action required.
	The Lily Foundation Charity	We think that although the remit does to some extent reflect the clinical issues in relation to LHON, we think it is a bit strange that there is no reference or comparison to Idebenone. We very much support the assessment of Lenadogene as it appears to show real promise as an effective treatment for LHON, however we are mindful that there is a significant minority of LHON patients (30-50%) who would not be eligible for this treatment as they have the 'wrong' mutation. On the basis of equity of access this really concerns us. If we are looking at the bigger picture for our entire LHON patient population, we think that ALL available treatment options should be considered alongside each other, and we believe a comparator assessment of Idebenone could open up a really valuable opportunity to develop a proper care-pathway for the disease	Thank you for your comment. Idebenone is due to be considered for evaluation by NICE topic selection. The scope has been updated to include idebenone as a comparator, subject to NICE topic selection and evaluation.

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		group as a whole, rather than looking as a single drug therapy, for a single mutation, in isolation, which we worry risks exacerbating health inequality. We would encourage NICE to consider evaluating Idebenone alongside Lenadogene for LHON patients, in to offer truly inclusive treatment options for patients with LHON.	
Timing Issues	GenSight Biologics SA	The lenadogene nolparvovec clinical data suggests that patients should be treated within 2 years of the onset of LHON. Any delay in the outcome of the appraisal will exclude some patients from treatment with lenadogene nolparvovec who would benefit from an improvement in visual acuity.	Thank you for your comment. No action required.
	Chiesi	There are currently few treatment options and no NICE guidance for LHON, therefore there is a significant unmet need for national guidance.	Thank you for your comment. No action required.
	Leber's Hereditary Optic Neuropathy Society	We consider this review to be urgent. This new technology potentially represents a step change in treatment of LHON for which there is no alternative for the vast majority of patients with the disease.	Thank you for your comment. No action required.
	United Kingdom Neuro-Ophthalmology Society	It should be reviewed within 6 months, as there is currently no treatment in England that is funded for this group of patients.	Thank you for your comment. No action required.
	The Lily Foundation Charity	We would consider this evaluation extremely urgent. Early intervention is crucial with LHON as natural history suggests loss of vision spreads rapidly to the second eye after onset, and severe visual loss can happen within a matter of months. This is devastating at any age but is especially cruel for teenagers which is the most common age of onset.	Thank you for your comment. No action required.

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Additional comments on the draft remit	Leber's Hereditary Optic Neuropathy Society	It is a little difficult to comment in detail on a remit that considers a treatment "within its marketing authorisation" when no such marketing authorisation exists and therefore we cannot comment on the contents and accuracy of that authorisation.	Thank you for your comment. No action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	GenSight Biologics SA	The draft scope specifies a range of 50% to 70% of people with an m.11778G>A mutation in the mitochondrial ND4 gene (Yu-Wai-Man et al., 2003, LHON Society, 2021, Meyerson et al., 2015). However, based on two recent papers, the m.11778G>A mutation could account for up to 75% of LHON in North America and Europe (Carelli et al., 2017, Yu-Wai-Man et al., 2016). Therefore, we suggest that the range is amended as 50% to 75%. (See also HST Checklist submitted to NICE — 19th May 2021).	Thank you for your comment. The background section has been updated.
	Chiesi	The accuracy of the information for use of idebenone should be updated to reflect that it is used in a small number of centres in England. Although idebenone is not routinely commissioned nationally by NHS England as stated in its commissioning policy, it is nevertheless in use locally by several NHS Trusts in England, who are self-funding this treatment despite a lack of national policy due to the high clinical need and the demand for this treatment by patients and clinicians. Idebenone has never been assessed by NICE and instead has had a long and complex history of seeking funding with the NHS, and the full clinical and economic data set has not been reviewed by either NICE or NHS England.	Thank you for your comment. The background section offers a brief explanation of the disease area and treatment options. No change required.

Section	Consultees	Comments	Action
		NICE originally considered topic-selection of idebenone but decided against it because of the challenges of defining small patient populations (this was prior to the introduction of the Highly Specialised Technologies Programme). Instead, initial assessment of idebenone was made directly by NHS England's specialised commissioning directorate via its prioritisation process. Despite having received a product licence via the EMA where efficacy was established,1 the Clinical Panel at NHS England concluded there was insufficient evidence to consider making the treatment available. The SMC in Scotland,2 AWMSG in Wales3 and NCPE in Ireland4 have all since concluded there was sufficient evidence to recommend idebenone. The decisions in England over the last six years have left patients without a treatment option – a significant disappointment to patients and their families and clinicians who were keen to access the treatment. Chiesi Ltd sought feedback from NHS England on the type and quality of evidence needed to secure reconsideration for funding. Chiesi has subsequently generated significant, new evidence, which is currently available. We believe this information should be included for completeness of understanding the treatment pathway.	

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	Leber's Hereditary Optic Neuropathy Society	The information is broadly accurate within the bounds of existing peer-reviewed publications. However, we would point out that the natural history of LHON is under-studied and in particular we would point to recent Australian research which calls into question some of the established thinking, in particular about the relative incidence between male/female and age profile of those first affected by LHON. https://www.sciencedirect.com/science/article/pii/S0002929721003517	Thank you for your comment. No action required.
	United Kingdom Neuro-Ophthalmology Society	The wording does reflect the severe sight loss these people experience. It should be noted that very rarely people of older age groups than defined in the wording my also develop visual loss and have positive genetic testing. It does not include the detrimental effects on mental health that are clinically recognised with a diagnosis of LHON.[Garcia 2017] Garcia GA, Khoshnevis M, Gale J, Frousiakis SE, Hwang TJ, Poincenot L, Karanjia R, Baron D, Sadun AA. Profound vision loss impairs psychological well-being in young and middle-aged individuals. Clin Ophthalmol. 2017 Feb 22;11:417-427	Thank you for your comment. No action required.
	NHS England Highly Specialised Commissioning	Idebenone has a marketing authorisation in the UK for LHON. However, it is not currently recommended for routine use in the NHS in England – this is technically incorrect – and should read that it is not commissioned rather than recommended and so it cannot be accessed	Thank you for your comment. The background section has been updated.
	The Lily Foundation Charity	Accurate	Thank you for your comment. No action required.

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The technology/ intervention	GenSight Biologics SA	The description (last paragraph, page 2) refers to the lenadogene nolparvovec clinical trials as using a placebo, this is the case for REFLECT, however the RESCUE and REVERSE clinical trials both used sham injections. Placebo refers to administration of an inert substance while sham is a procedure that mimics the actual procedure in every way. Please amend the technology description to: 'it has been studied in clinical trials, compared with placebo and sham'' Please add that lenadogene nolparvovec was granted EU orphan status in May 2011. Please add that lenadogene nolparvovec was granted EU ATMP classification — Gene therapy medicinal product in April 2018.	Thank you for your comment. The technology section has been updated.
	Leber's Hereditary Optic Neuropathy Society	Yes, insofar as we are in a position to judge as patients.	Thank you for your comment. No action required.
	United Kingdom Neuro-Ophthalmology Society	Yes	Thank you for your comment. No action required.
	The Lily Foundation Charity	Accurate	Thank you for your comment. No action required.
Population	GenSight Biologics SA	Yes, the population is defined appropriately. There are no sub groups that should be considered separately.	Thank you for your comment. No action required.

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	Chiesi	The population for lenadogene nolparvovec seems defined appropriately. Chiesi Ltd would like to highlight that 30%-50% of LHON patients do not have the G11778A ND4 mitochondrial mutation who currently and in future will have no access to any treatment due to the lack of assessment of idebenone. Idebenone is licensed to treat all patients with LHON, therefore would provide a treatment option for the entire LHON population	Thank you for your comment. Idebenone will not be considered as part of this highly specialised technology evaluation. No action required.
	Leber's Hereditary Optic Neuropathy Society	Please see the comment above regarding incidence. The intervention targets only one mutation causing sight loss from LHON and of course it is appropriate to only consider patients in that group, notwithstanding the fact that this will not directly benefit those harbouring other LHON causing mutations. However, it is hoped that those other groups will benefit in future from this work as it is built upon and expanded to other mutations or even mutation-agnostic variants.	Thank you for your comment. No action required.
	United Kingdom Neuro-Ophthalmology Society	They have not defined the time period of disease start or sight loss.	Thank you for your comment. The population section states the anticipated population only. No action required.

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	NHS England Highly Specialised Commissioning	Is this all ages or adults only? If this is an inherited condition would it be possible to define optimal time for testing and treating? Understanding of benefits for patients with sight loss over twelve months And estimate of the incident population annually would be beneficial for service planning	Thank you for your comment. The population section states the anticipated population only. No action required.
	The Lily Foundation Charity	Accurate, but the G11778A mutation only represents 50%-70% of the LHON patient population, so in isolation, Lenadogene will not offer a treatment option for everyone with LHON.	Thank you for your comment. No action required.
Comparators	GenSight Biologics SA	Yes	Thank you for your comment. No action required.
	Chiesi	No - idebenone should be included as a comparator. Despite the lack of NHS England funding, idebenone is the only product with a specific marketing authorisation for LHON and the only active treatment option in England, where some Trusts have been prepared to fund treatment with idebenone following requests from specialists. Idebenone is also the standard of care for patients with LHON in Wales, Scotland and Ireland.2,3 As a proportion of the LHON population are currently being treated with idebenone in England, and it is the current standard of care in Wales, idebenone should be included as a valid comparator in this appraisal.	Thank you for your comment. Idebenone is due to be considered for evaluation by NICE. The scope has been updated to include idebenone as a comparator, subject to NICE topic selection and evaluation..

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	Leber's Hereditary Optic Neuropathy Society	Yes. There is effectively no other treatment approved in England, which represents the majority of cases in the UK. Idebenone is approved but not reimbursed by NHSE and we do not believe that use of a non-reimbursed comparator would be appropriate nor especially informative. In Scotland and Wales there is a potential comparator and we are aware that some in England are able to access the treatment by obtaining generic versions of idebenone OTC without proper medical supervision, but for the above reasons we do not believe this would be appropriate nor feasible to use as a comparator.	Thank you for your comment. Idebenone is due to be considered for evaluation by NICE. The scope has been updated to include idebenone as a comparator, subject to NICE topic selection and evaluation.
	United Kingdom Neuro-Ophthalmology Society	These current strategies are used in England, but not Scotland or Wales which have access to Idebenone.	Thank you for your comment. Idebenone is due to be considered for evaluation by NICE. The scope has been updated to include idebenone as a comparator, subject to NICE topic selection and evaluation.
	NHS England Highly Specialised Commissioning	Supportive treatment only available in the NHS no other treatment available at this time	Thank you for your comment. Idebenone is due to be considered for evaluation by NICE. The scope has been updated to include idebenone as a comparator, subject to NICE topic selection and evaluation.

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	The Lily Foundation Charity	Accurate, but this does not include comparison with Idebenone which is licenced and used in Wales, Scotland and many European countries successfully to treat LHON patients and is not restricted to a single mutation. We believe this should be considered as a comparison.	Thank you for your comment. Idebenone is due to be considered for evaluation by NICE. The scope has been updated to include idebenone as a comparator, subject to NICE topic selection and evaluation.
Outcomes	GenSight Biologics SA	No GenSight Biologics did not collect any clinical data on 'visual evoked potentials' during the REFLECT, REVERSE or RESCUE trials. Therefore, we request that this outcome removed from the scope.	Thank you for your comment. 'Visual evoked potentials' has been removed as an outcome.

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	Leber's Hereditary Optic Neuropathy Society	There are considerable mental health impacts from this condition which will not be captured by these measures, which is a clear limitation. However, as at this moment there are no effective tools that we are aware of that would provide the needed evidence and work must be done to build these. QoL might be thought to address these points, but not really - for patients who are prevented from losing vision, for example, they may not see an improvement in the event of successful treatment but would most certainly see deterioration in the event there was no intervention or it was ineffective. All too frequently neglected is the anxiety caused by those who are not even affected (directly) by LHON but are known carriers of the disease and must live with the reality that this could strike them at any time without warning. This has been said by some (subsequently affected) carriers to be in some ways worse than when they became affected. As for other outcome measures, we also consider these to be inadequate for a condition that typically results in off-chart vision, but as we have nothing to offer as an alternative (for now, anyway) we have to accept them as appropriate. We are actively working with expert clinicians to develop and validate better outcome measures but this will of course take time.	Thank you for your comment. No action required.
	United Kingdom Neuro-Ophthalmology Society	Instead of retinal nerve fibre layer/macular thickness, I believe these could be more accurately described: Optical coherence tomography measures including the peripapillary retinal nerve fibre layer; and the macula ganglion cell layer volume or macula ganglion cell complex layer height.	Thank you for your comment. Outcomes are kept broad on the scope. No action required.

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	NHS England Highly Specialised Commissioning	Consider Impact on daily life	Thank you for your comment. Impact on daily life is captured in the 'health-related quality of life' outcome. No action required.
	The Lily Foundation Charity	Accurate	Thank you for your comment. No action required.
Economic analysis	GenSight Biologics SA	Lenadogene nolparvovec causes a permanent change in the mitochondrial organelle, therefore a lifelong time horizon is appropriate to assess this product. We propose a cost-utility analysis across a lifetime horizon to capture the incremental costs and QALYs accrued over patients' lives.	Thank you for your comment. No action required.
	Chiesi	To ensure the economic analysis is sufficiently long enough to capture any differences in costs and outcomes, the time horizon should be a lifetime horizon. In the case of LHON, visual impairment and blindness occur rapidly following onset of symptoms, last a lifetime and have a significant impact on the cost of blindness and quality of life of the patient.	Thank you for your comment. No action required.

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	Leber's Hereditary Optic Neuropathy Society	Time horizon for assessment seems unclear to us and, indeed, it is not yet known how long-lasting any benefits will be, but they are assumed to be multi-year and perhaps even life-long. It is not clear from the text how the difference between best and worst performing eye will impact the assessment. In our view, while we would obviously prefer to see both eyes improve, the benefit of just one eye improving in a meaningful way is potentially vast - binocular vision is a plus but we would hate to see too much focus (sic) on this. Therefore we note the comment regarding best and worst seeing eye analysis and consider it vital that cost effectiveness analysis should be based on the benefit to the best seeing eye, which would be seen as highly beneficial by LHON patients.	Thank you for your comment. No action required.
	United Kingdom Neuro-Ophthalmology Society	The economic analysis should be over the course of the affected person's life. Whilst we acknowledge the economic modelling will include the cost of the genetic testing, it should be born in mind that we probably over investigate people with sight loss to include the LHON genetic tests (main 3 mutations) in people who are unlikely to have the phenotype already in England. Hence I do not believe this should be a specific burden, as it is standard of care in this clinical situation and there is no clinical definite way to diagnose LHON.	Thank you for your comment. No action required.
	NHS England Highly Specialised Commissioning	Cost effectiveness should include cost of access for pre-screening, access and monitoring and follow up. Plus, an analysis of service implications to include managing capacity through staff training, patient counselling, preparation storage and disposal	Thank you for your comment. No action required.

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	The Lily Foundation Charity	For patients living with LHON, any improvement, can be lifechanging. It can be the difference between social interaction and depressive isolation. It can be the difference between independent living and residential care. All of these variables have a significant economic impact which I am unclear is being evaluated?	Thank you for your comment. These factors will be captured within the health-related quality of life outcome. No action required.
Equality	GenSight Biologics SA	If NICE proceeds to scoping on the basis that lenadogene nolparvovec will be available to all patients with Leber's hereditary optic neuropathy caused by the m.11778G>A mutation in the mitochondrial ND4 gene, we do not consider that the proposed remit and scope will need to be amended to meet NICE's equality aims.	Thank you for your comment. No action required.

Section	Consultees	Comments	Action
	Chiesi	Until NICE assesses all available treatments for LHON it is unfortunately perpetuating a historical issue of inequity of access to treatment. Exclusion of idebenone from the NICE process precludes consideration of a pharmacological treatment for all LHON patients, including the 30-50% of people with LHON without G11778A ND4 who are not appropriate for treatment with lenadogene nolparvovec. Without pharmacological treatment this subgroup of patients with LHON are left severely visually impaired and at high risk of early blindness, with all the associated patient and societal burden of such a life-changing disability. The challenges around previous (non) assessment of idebenone relate to processes and methods of assessment of ultra-rare conditions that have since moved on – developed to be better able to assess evidence in very small patient groups. To continue to deny patients the chance to have their potential treatment option, assessment using similar methodologies perpetuates an established inequity.	Thank you for your comment. Idebenone will not be considered as part of this highly specialised technology evaluation. No action required.

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	Leber's Hereditary Optic Neuropathy Society	We do not believe that under the terms of this remit there are any equality issues raised by the proposed assessment. There are inevitably small variances in incidence and prevalence according to ethnic background but these are not directly relevant to the proposals. Income inequality is an issue, especially with the current situation where those with adequate resources can obtain supplies of the existing approved (but not reimbursed) treatment whereas those in lower income strata are significantly disadvantaged. We have already commented on the outdated nature of the natural history data and we would suggest that the traditional 5:1 ratio of male:female patients is treated with caution. Therefore we would like to see a higher proportion of female participation in any studies, perhaps as much as 30% of participation, and for efforts to be made to incorporate paediatric and older populations.	Thank you for your comment. No action required.
	United Kingdom Neuro-Ophthalmology Society	We do not believe there are biased groups here per se, except that those with an alternate mutation from Lebers causing sight loss and for which currently there is no data due to the inclusion criteria for the clinical trials. Inclusion should also remember those people who do not access NHS care and how to reach them. More specifically if granted access those in groups whom would be disadvantaged due to geography if having only a number of recognised centres delivering this specialist treatment.	Thank you for your comment. No action required.
	NHS England Highly Specialised Commissioning	This would have a positive impact on disability by reducing the number of people disabled through blindness	Thank you for your comment. No action required.

Section	Consultees	Comments	Action
	The Lily Foundation Charity	As previously mentioned, we recommend that Idebenone is considered alongside Lenadogene to ensure the entire LHON disease population has equal access to treatments that have the potential to transform their lives. Patients with LHON currently have to live with the harsh reality that their vision will get progressively worse until they go blind. These therapies offer LHON patients the first glimpse of hope that they may not have to follow the natural history of this disease. Please do not restrict this hope to a single gene mutation, but instead extend it to as many LHON patients as possible by enabling a comprehensive care pathway to be implemented for LHON which includes all comparators.	Thank you for your comment. Idebenone will not be considered as part of this highly specialised technology evaluation. No action required.
Innovation	GenSight Biologics SA	Lenadogene nolparvovec is a step change in the management of the condition because currently there are no routine treatments available for LHON, apart from best supportive care. Lenadogene nolparvovec is a first-in-class gene therapy that works by leveraging a mitochondrial targeting sequence (MTS) proprietary technology platform, arising from research conducted at the Institut de la Vision in Paris, which, when associated with the gene of interest, allows the platform to specifically address defects inside the mitochondria using an AAV vector (Adeno-Associated Virus). In lenadogene nolparvovec-treated patients, the BCVA showed a progressive and sustained improvement in both eyes, from Month 12 to Month 52, demonstrating a statistically significant and	Thank you for your comment. No action required.

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		clinically relevant treatment effect, persistent up to more than 3 years on average. This persistence of the effect was also shown up to Year 5 in the very first patients who received treatment. Importantly, at Month 48 (M48) and at the last available BCVA, the comparison of BCVA demonstrated a clinically relevant difference in BCVA in favour of treated eyes. Notably, most treated eyes were on-chart at M48 and at the last available BCVA, compared to less than half natural history treated (NHx) eyes. Similarly, the same analyses applied on best and worst eyes showed consistent results and all performed sensitivity analyses, controlling potential confounding factors (Age, Gender, Follow-up time) confirmed the robustness of the indirect comparison results. The Rescue and Reverse efficacy pools displayed similar and consistent favourable results compared to the NHx pool. It is very important that the severity of the disability is considered when calculating the QALY. The data for calculating a severity score will be taken from published literature.	
	Chiesi	Lenadogene nolparvovec has the potential to be effective in the sub-group of patients with the G11778A ND4 mutation. Effective treatments for LHON are a step-change as they represent the first opportunity to significantly alter the course of the condition. As a result, all licensed / available treatments should be assessed by NICE.	Thank you for your comment. Only lenadogene nolparvovec will be considered as part of this highly specialised technology evaluation. No action required.

Section	Consultees	Comments	Action
	Leber's Hereditary Optic Neuropathy Society	We do regard this as potentially a step change in treatment of this condition but remain anxious to see robust evidence of its beneficial effect and longevity. Due to the highly innovative nature of the intervention we are pleased to see it treated as a highly specialised technology as this to us seems entirely appropriate. We have mentioned previously the potential mental health benefits that are currently difficult or even impossible to capture. To these we might add the additional health complications (so-called "LHON+") that is even less understood or studied. We do not believe it is possible, therefore, to incorporate this into an HTA directly, but we still need to "park" these observations.	Thank you for your comment. No action required.
	United Kingdom Neuro-Ophthalmology Society	I do believe this would provide a stepwise change in the care of people with LHON and the 11778 mutation. The QALY calculation may not necessarily consider the full social care funding and inability to work that a person with LHON might experience. LHON affects young people and those of working age predominately.	Thank you for your comment. No action required.
	NHS England Highly Specialised Commissioning	Yes – there is currently no other alternative therefore a step change in the management of the condition. This is a step change Yes Not known	Thank you for your comment. No action required.
	The Lily Foundation Charity	Accurate	Thank you for your comment. No action required.

Section	Consultees	Comments	Action
Other considerations	GenSight Biologics SA	The draft scope states. "If the evidence allows the following subgroups will be considered. These include those with recent vision loss". This was not a pre-specified sub -groups so should be removed from the scope.	
Questions for consultation	GenSight Biologics SA	Have all relevant comparators for lenadogene nolparvovec been included in the scope? Yes All relevant comparators have been included. Which treatments are considered to be established clinical practice in the NHS for LHON? Best supportive care — established clinical management including visual aids, occupational/low vision rehabilitation and lifestyle management. Should outcomes related to the non-vision related symptoms of LHON be included? Yes GenSight Biologics suggest that the assessment should include non-vision related symptom outcomes such as mental health including depression, social impact, carer burden, disability, employment and productivity, education, transport and mobility, as per the RNIB report on economic impact of sight loss. (https://www.rnib.org.uk/professionals/knowledge-and-research-hub/research-reports/general-research/economic-impact-sight-loss).	Thank you for your comment. No action required.

Section	Consultees	Comments	Action
		Are there any subgroups of people in whom lenadogene nolparvovec is expected to be more clinically effective and cost effective or other groups that should be examined separately? No What percentage of people with LHON present with the G11778A ND4 mutation? The draft scope specifies a range of 50% to 70% of people with an m.11778G>A mutation in the mitochondrial ND4 gene (Yu-Wai-Man et al., 2003, LHON Society, 2021, Meyerson et al., 2015). However, based on two recent papers, we believe that the m.11778G>A mutation could account for up to 75% of LHON in North America and Europe (Carelli et al., 2017, Yu-Wai-Man et al., 2016). Therefore, we suggest that the range is amended as 50% to 75%. (See also HST Checklist submitted to NICE — 19th May 2021) To what extent are people with LHON currently tested for the G11778A ND4 mutation in clinical practice in the NHS? All suspected LHON patients have their diagnosis confirmed by a genetic test. This test can be undertaken in specialist ophthalmology centres.	

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	Chiesi	Chiesi Limited are of the view that not all relevant comparators have been included (see response above) and also that NICE should undertake a health technology evaluation of idebenone for LHON. A summary of the history and changes in treatment pathway, availability of new clinical data and desire of patients and clinicians for funding is outlined below.	Thank you for your comment. Idebenone will not be considered as part of this highly specialised technology evaluation. No action required.
	Leber's Hereditary Optic Neuropathy Society	We would point to some interesting work, IRD Counts, undertaken under the auspices of Retina UK on the economic cost of vision loss, which does incorporate some additional health costs that are not traditionally captured using conventional tools. Whilst regrettably LHON was not included in this analysis, it is relatively straightforward and legitimate to extrapolate the data for, eg Stargardts Disease, to LHON patients. https://www2.deloitte.com/content/dam/Deloitte/au/Documents/Economics/deloitte-au-economics-cost-illness-irds-uk-030919.pdf	Thank you for your comment. No action required.

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	United Kingdom Neuro-Ophthalmology Society	Comparators in England have been stated accurately Comparators for the UK include idebenone. See outcomes as annotated above The clinical trials have not addressed the non-visual outcomes, and hence should not be considered here in terms of outcomes unless new evidence is available. The clinical trials were in 11778. Whilst there is sparse specific data on those with a new diagnosis of 11778 annually in England one would expect less than 1 per million of the population I believe that most people should be tested for the main three mutations, and that clinical practice has improved in this regard over the last decade. I do not believe there are any specific groups that are inherent disadvantaged over this treatment, other than those with different LHON mutations in whom there is currently no trial data to support use in these groups.	Thank you for your comment. Idebenone will not be considered as part of this highly specialised technology evaluation. No action required.
Additional comments on the draft scope	Chiesi	Idebenone has a long and complex history for access for patients in the UK. There is now a huge inequity of access to treatment for LHON patients across the UK. Idebenone is funded and accessible in Scotland and Wales but patients in England are still left without treatment options. NICE originally considered topic-selection of idebenone in 2011 (in the days prior to the establishment of the Highly Specialised Technology programme) and decided not to appraise it due to difficulties in defining the small patient population.5 Since gaining a marketing authorisation in 2015, idebenone has been routed through the NHS England specialised commissioning process. Despite having received a product licence via the EMA where	Thank you for your comment. Idebenone will not be considered as part of this highly specialised technology evaluation. No action required.

Commented [EL1]: Do I need to respond with more detail to this comment?

Section	Consultees	Comments	Action
		efficacy was established, the Clinical Panel at NHS England concluded there was insufficient evidence to consider making the treatment available. The treatment therefore did not progress beyond the 'Clinical Build' phase (the first of the process's three stages) and was never considered by CPAG. After Chiesi acquired the treatment from Santhera a second attempt by clinicians to have a clinical commissioning policy developed (in 2020) was again rejected by NHS England (January 2021) on the grounds of lack of evidence for efficacy. Despite the clinical evidence being deemed as efficacious by the EMA, SMC in Scotland, AWMSG in Wales and NCPE in Ireland. Over the course of six years these decisions in England have left patients without a treatment option and to progress to vision loss and blindness – a significant disappointment to patients and their families and clinicians who were keen to access the treatment. Chiesi Ltd sought feedback from NHS England on the type and quality of evidence needed to secure reconsideration for funding. Chiesi has subsequently generated significant, new evidence, which is currently available and is now just awaiting final publication. Originally, when idebenone was considered at NICE, the clinical evidence base was more limited than it is now, and processes and methods were not set in place to review rare diseases. We are now in a position where post-authorisation studies for idebenone have been completed and publications are expected in 2023. In addition to this, NICE is well equipped to undertake a technology appraisal for idebenone considering the comprehensive data set. With the positive results of the LEROS trial6 and the recent approval of idebenone by AWMSG3 and by	

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		the SMC,2 Chiesi Limited considers that a NICE assessment is now not only feasible but would enable a fair consideration of all the evidence (including unpublished and economic evidence) for idebenone. A NICE assessment would enable the opportunity for timely and equitable access to idebenone for all patients with LHON in England who currently have no treatment options available to them. Chiesi are of the view that NICE should now consider idebenone as a HST assessment to resolve the issue of funding and availability of idebenone once and for all.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

List here