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Clinical science

Efficacy of lenadogene nolparvovec gene therapy versus idebenone in Leber hereditary optic neuropathy due to the m.11778G>A *MT-ND4* variant: two matching adjusted indirect comparisons

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bjo-2025-329206).

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Received 3 December 2025
Accepted 6 April 2026

ABSTRACT

Background Lenadogene nolparvovec is an intravitreal gene therapy for patients with Leber hereditary optic neuropathy (LHON) carrying the m.11778G>A *MT-ND4* variant. Idebenone, a synthetic coenzyme Q_{10} analogue, is the only approved treatment for LHON. To estimate the relative effects of both treatments, we performed two matching adjusted indirect comparisons (MAICs) between idebenone aggregated data from the LEROS study and expanded access programme (EAP), and lenadogene nolparvovec individual data from the REFLECT study (bilateral treatment).

Methods Matching covariates included age at disease onset, sex, baseline best-corrected visual acuity (BCVA), and time from vision loss to treatment. The outcomes of interest were clinically relevant recovery (CRR) from nadir at 24 months, time to initial CRR and change from baseline BCVA at 24 months.

Results For the MAIC LEROS versus REFLECT (effective sample size (ESS): 77), a statistically higher CRR at 24 months was observed with lenadogene nolparvovec compared with idebenone (60.4% vs 35.4%; OR=2.78, 95% CI 1.53 to 5.06; p=0.001). No statistically significant difference was observed for time to initial CRR and change from baseline BCVA at 24 months. For the MAIC EAP versus REFLECT, there was a low overlap between the two populations related to a difference in the time from vision loss to treatment. In a post hoc sensitivity analysis comparing EAP to RESCUE data (ESS: 33), CRR was 39.0% for idebenone versus 69.5% for lenadogene nolparvovec (OR=3.59, 95% CI 1.42 to 9.06; p=0.011).

Conclusion The two MAICs demonstrated a clinically meaningful higher visual recovery at 24 months with lenadogene nolparvovec than with idebenone in patients with LHON due to the m.11778G>A *MT-ND4* variant.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Idebenone is the only approved treatment for Leber hereditary optic neuropathy (LHON). Lenadogene nolparvovec is not yet approved as an intravitreal gene therapy for patients with LHON due to the m.11778G>A *MT-ND4* variant. Data comparing these two therapeutic options is limited.

WHAT THIS STUDY ADDS

⇒ The two matching adjusted indirect comparisons comparing idebenone and lenadogene nolparvovec demonstrated a higher clinically meaningful visual recovery at 24 months with lenadogene nolparvovec compared with idebenone.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Lenadogene nolparvovec is a promising and effective therapeutic option for patients with *MT-ND4* LHON.

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To cite: Yu-Wai-Man P, Newman NJ, Carelli V, *et al*. *Br J Ophthalmol* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/bjo-2025-329206

INTRODUCTION

Leber hereditary optic neuropathy (LHON) is a rare mitochondrial disorder characterised by acute/subacute bilateral vision loss, which in most cases persists throughout life.[1 2] This maternally inherited condition is caused by variants in mitochondrial DNA, most commonly affecting the genes encoding the subunits of complex I of the mitochondrial respiratory chain.[3] The three primary disease-causing variants—11778G>A in *MT-ND4*, 3460G>A in *MT-ND1* and 14484T>C in *MT-ND6*—account for approximately 90% of LHON cases.[3] A growing number of nuclear genes have also been reported to cause autosomal recessive LHON.[4]

LHON selectively targets retinal ganglion cells, leading to their degeneration and subsequent optic nerve atrophy.[5] Hence, the phenotype of the disease is largely monosymptomatic with visual loss as its defining clinical feature.[1] Not all patients carrying a mitochondrial DNA variant associated with LHON will develop visual loss.[1] The variable penetrance and male predominance of the disease suggest the involvement of additional genetic, hormonal and/or environmental factors in its expression.[6–8]

The only approved treatment to date for LHON is idebenone (Raxone, Chiesi Farmaceutici), a synthetic analogue of coenzyme Q_{10}, which acts as an electron shuttle able to bypass dysfunctional complex I of the electron transport chain. Idebenone has been approved in Europe since 2015 at a dose of 900 mg/day for the treatment of LHON, regardless of the causative variant.[9] Data from a retrospective

observational study and an expanded access programme (EAP) showed that patients were more likely to recover if idebenone was initiated within 12 months of vision loss and treatment provided for at least 24 months.[10 11] Recently, the results of the non-randomised controlled LEROS study demonstrated that idebenone was effective in improving visual function or stabilising vision at 12 and 24 months in 181 patients treated within 5 years of symptom onset, compared with a matched external natural history cohort.[12] It has also been recently clarified that two polymorphic variants in the gene encoding the enzyme NQO1 affect idebenone efficacy, providing a potential explanation for the lack of response in ~50% of treated patients.[13] NQO1 is key to presenting idebenone in its therapeutically effective reduced form.

Differently, lenadogene nolparvovec is an intravitreal gene therapy product designed for patients with LHON due to the m.11778G>A *MT-ND4* variant, which intends to permanently correct the underlying causative genetic defect. In two randomised phase 3 studies, 76 patients with vision loss ≤6 months (RESCUE[14]) or between 6 and 12 months (REVERSE[15]) were treated with a single unilateral intravitreal injection of gene therapy versus a sham injection. In another phase 3 randomised, placebo-controlled study (REFLECT), 98 participants with vision loss duration ≤12 months received a single injection of lenadogene nolparvovec in their first-affected eye and either a second injection of lenadogene nolparvovec or a placebo injection in their second-affected eye.[16] These three studies revealed an unexpected contralateral effect, in which the eye treated with sham or placebo showed an improvement in best-corrected visual acuity (BCVA) alongside the treated eye.[14–16] Persistence of the benefit from lenadogene nolparvovec was demonstrated until 5 years post-treatment.[17] To provide further evidence of the efficacy of lenadogene nolparvovec, visual acuity data from 174 *MT-ND4* patients from the phase 3 studies were pooled and compared with an external control group of 208 untreated patients, showing a statistically significant improvement in final BCVA in favour of gene therapy over natural history.[18]

To determine the relative treatment effects of lenadogene nolparvovec and idebenone, we performed two matching adjusted indirect comparisons (MAICs), namely, LEROS versus REFLECT and EAP versus REFLECT.

MATERIALS AND METHODS

Data sources

Idebenone studies were first identified through a systematic literature search and additional targeted searches and then assessed in terms of requirements and concordance for inclusion in the MAICs. The main inclusion criteria were a timing of treatment initiation (idebenone) or injection (lenadogene nolparvovec) ≤1 year post vision loss and the availability of outcomes of interest.

The first MAIC was performed using trial-level aggregated data (AD) from the LEROS study[12 19] and individual patient data (IPD) from the REFLECT study.[16] The second MAIC was performed using trial-level AD from the EAP programme and IPD from the REFLECT study. Data from the LEROS study were extracted from the GBA dossier of Santhera Pharmaceuticals,[19] which provided more detailed information than the publication.[12] Data from the EAP study were obtained from the publication of *Catarino and colleagues*.[11]

For the sensitivity analyses, IPD from the RESCUE[14] and REVERSE[15] studies were pooled to the IPD from REFLECT, constituting the lenadogene nolparvovec pool.

Outcomes

The predefined outcomes of interest were clinically relevant recovery (CRR) from nadir at 24 months, time to an initial CRR among the responders and change of logarithm of the minimum angle of resolution (LogMAR) from baseline at 24 months. As the LogMAR change from baseline was not available in the publication from *Catarino and colleagues*,[11] the MAIC comparing EAP to REFLECT only assessed the CRR from nadir and the time to an initial CRR. In all studies, the outcomes were provided in the *MT-ND4* population treated ≤1 year after the onset of symptoms.

The definition of CRR was similar between lenadogene nolparvovec and idebenone studies: an on-chart BCVA gain of at least 10 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters, which corresponds to an improvement of at least 0.2 LogMAR, or a conversion from off-chart to on-chart BCVA. A patient had a CRR if at least one eye had a CRR. If a patient/eye showed a CRR at a follow-up visit prior to 2 years, but not at 2 years, they were not considered a responder and no CRR was considered. All studies defined the time to an initial CRR as the time when the first CRR occurred.

In the lenadogene nolparvovec studies, the equivalence in LogMAR followed the Lange recommendations.[20] To ensure comparability with idebenone data, the off-chart values of the gene therapy studies were rescaled according to the rules used in LEROS and EAP, where patients with particularly poor visual performance, that is, off-chart, including counting fingers, hand motion and light perception, were assigned the value +1.8 LogMAR.[11 12 19]

Some minor differences should be noted between the lenadogene nolparvovec and idebenone studies in terms of LogMAR assessments at ETDRS scale. For lenadogene nolparvovec studies, an eye with a LogMAR ≤ +1.60 was considered on-chart; that is, at least 3 letters read on the first line of the ETDRS chart (approach row by row; score ETDRS: LogMAR ≤ +1.64 (at least 3 letters read) was considered on-chart; score ETDRS: LogMAR +1.66 (2 letters read) or +1.68 (1 letter read) was considered off-chart); for idebenone studies, an eye with a LogMAR ≤ +1.68 was considered on-chart; that is, at least 1 letter read on the first line of the ETDRS chart (score ETDRS ≤ +1.68). Additionally, for lenadogene nolparvovec studies, a move from off-chart to on-chart was a move from LogMAR ≥ +1.66 (no letter or one letter or two letters read) to LogMAR ≤ +1.60 (at least three letters read), and for idebenone studies, a move from off-chart to on-chart was a move from LogMAR > +1.68 (no letter read) to LogMAR ≤ +1.60 (at least five letters read). These differences in LogMAR reporting were balanced between the two products. Improvement from baseline in LogMAR favoured idebenone (eg, an improvement from +1.64 to +1.60 LogMAR was assessed as an improvement of −0.04 LogMAR for idebenone and no improvement (0 LogMAR change) for lenadogene nolparvovec). On the other hand, switch from off-chart to on-chart favoured lenadogene nolparvovec. For example, a move from LogMAR +1.68 to +1.60 was considered to be a move from off-chart to on-chart for lenadogene nolparvovec, whereas for idebenone, it was not considered to be a move from off-chart to on-chart, but an on-chart improvement of −0.08 LogMAR.

Matching variables

Weights were assigned to the population with available IPD (lenadogene nolparvovec patients) to match the baseline AD of the idebenone population with which it was compared. The

patients' baseline characteristics used as matching variables included age at onset of symptoms, sex, baseline BCVA and time from vision loss to treatment initiation/injection.

Baseline characteristics were described for weighted and unweighted populations. Sex was compared using a χ^2 test, while age at onset, baseline BCVA and time from vision loss to treatment were compared using univariate t-tests.

Unanchored matching adjusted indirect comparisons

Two separate unanchored analyses were performed using a direct matching of the LEROS results[12 19] to REFLECT data and the results of the EAP reported by *Catarino and colleagues*[11] to those of REFLECT. The weights of the lenadogene nolparvovec IPD were estimated using a logistic propensity score model. Due to the lack of IPD in the idebenone selected studies, according to the National Institute for health and Care Excellence(NICE) recommendations, the method of moments was used to balance the mean covariate values across populations.[21 22] The effective sample size (ESS) was presented.

The outcomes of interest for lenadogene nolparvovec were predicted by reweighting the observed outcome from the studies. To compare CRR between the treatment arms, a χ^2 test was used and OR with 95% CI was calculated. A univariate t test was used to compare the LogMAR change from baseline and the time to an initial CRR.

RESULTS

MAIC LEROS versus REFLECT

Baseline IPD from REFLECT for the subgroup of eyes treated bilaterally with lenadogene nolparvovec (n=96 eyes) was weighted to match baseline AD from eyes treated with idebenone within 1 year after disease onset in LEROS, regardless of their causative mitochondrial DNA variant (n=218 eyes). Before matching, age at onset of first symptoms and sex distribution were similar between idebenone and lenadogene nolparvovec arms (table 1). Conversely, baseline BCVA was statistically significantly more impaired in lenadogene nolparvovec patients compared with idebenone patients (1.42 (0.38) vs 1.24 (0.53) LogMAR, p=0.002), and time from vision loss (at eye level) to treatment initiation/injection was statistically significantly longer in patients treated with gene therapy than patients treated with idebenone (7.4 (3.5) vs 6.5 (4.4) months, p=0.035). After matching, the ESS of the lenadogene nolparvovec arm was 77, that is, 91% of the original sample, and baseline characteristics were similar between the two treatment arms, with a mean baseline BCVA of 1.24 LogMAR and a mean time from vision loss to treatment of 6.5 months for both arms (table 1).

The main analysis of the MAIC showed that lenadogene nolparvovec was associated with a statistically significantly higher CRR compared with idebenone (60.4% vs 35.4%; p=0.001), with an OR (95% CI) of 2.78 (1.53 to 5.06) (CRR at eye level) (table 2). Results of all sensitivity analyses were consistent with the results of the main analysis (online supplemental table 1 and figure 1).

The leave-one-out analysis showed that removing any of the baseline characteristics from the propensity score base case model did not change the pattern of significance in the relative treatment effects and it yielded comparable point estimates. Sensitivity analysis using the single baseline BCVA matching covariate in the *MT-ND4* population showed similar results to the main analysis, with an OR (95% CI) of 2.97 (1.63 to 5.38) in favour of lenadogene nolparvovec (table 2).

Comparing the pooled lenadogene nolparvovec data with the LEROS data, all results were consistent with those of the main analysis (online supplemental table 1). No statistically significant difference between lenadogene nolparvovec and idebenone eyes was observed for the time to initial CRR and the change from baseline BCVA at 24 months in all analyses (table 2).

The sensitivity analysis using the LEROS method for ETDRS BCVA assessment on REFLECT data revealed similar results to those of the main analysis (online supplemental table 2).

MAIC EAP versus REFLECT

Baseline IPD from REFLECT for the subgroup of patients treated bilaterally (n=48 patients) was weighted to match baseline AD from LHON patients with *MT-ND4* variant treated with idebenone in EAP (n=54 patients). Before matching, age

Table 1 Baseline characteristics of unmatched and matched populations: LEROS (n=109 patients) versus REFLECT bilateral (n=48 patients)

	Idebenone patients (LEROS)	Lenadogene nolparvovec patients unweighted	P value unweighted	Lenadogene nolparvovec patients weighted	P value weighted
N eyes	218	96		87.1	
Age at onset of first symptoms (years)					
Mean (SD)	33.4 (15.0)	31.7 (14.3)	0.82	33.4 (13.9)	0.50
Min–Max	12.0–78.2	14.0–73.0		14.0–73.0	
Sex					
Male (%)	156 (71.6%)	74 (77.1%)	0.38	62.3 (71.5%)	1.00
Female (%)	62 (28.4%)	22 (22.9%)		24.8 (28.5%)	
Baseline BCVA (LogMAR) (eye level)*					
Mean (SD)	1.24 (0.53)	1.42 (0.38)	**0.002**	1.24 (0.46)	0.50
Min–Max	–	0–1.8		0–1.8	
Time from vision loss to treatment injection/initiation (months) (eye level)* †					
Mean (SD)	6.5 (4.4)	7.4 (3.5)	**0.035**	6.5 (3.8)	0.50
Min–Max	–	0.03–12.0		0.03–12.0	

The baseline characteristics of LEROS patients were obtained from the subgroup of patients with Leber hereditary optic neuropathy due to any variant treated ≤1 year after the onset of symptoms (n=109 patients; 218 eyes).
Bold entries indicate p-values <0.05.
*Baseline BCVA and time from vision loss to treatment were calculated at eye level.
†Time from vision loss was defined as the time from symptoms onset at eye level (time from symptoms for each eye separately).
BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution.

Table 2 Outcomes with idebenone (LEROS) versus lenadogene nolparvovec (REFLECT bilateral or lenadogene nolparvovec pool)

		Idebenone (LEROS)	Lenadogene nolparvovec	P value OR (95% CI) if applicable	ESS
	N eyes	**110**	**96**		
CRR from nadir at 24 months*					
Naïve analysis†	N	96	96	**<0.001** 3.18 (1.76 to 5.73)	NA
	CRR	34 (35.4%)	61 (63.5%)		
	Missing data	14	0		
Main analysis	N	96	87.1	**0.001** 2.78 (1.53 to 5.06)	77
	CRR	34 (35.4%)	52.6 (60.4%)		
	Missing data	14	0		
Sensitivity analysis (baseline BCVA in *MT-ND4* population)	N	96	90.6	**0.001** 2.97 (1.63 to 5.38)	85
	CRR	34 (35.4%)	56.1 (61.9%)		
	Missing data	14	0		
Sensitivity analysis (Lenadogene nolparvovec pool)	N	96	308.4	**<0.001** 2.98 (1.85 to 4.81)	275
	CRR	34 (35.4%)	191.4 (62.1%)		
	Missing data	14	7		
Time to initial CRR (months)*					
Naïve analysis†	N	34	61	0.72	NA
	Mean (SD)	10.3 (6.7)	9.3 (8.7)		
	Min–Max	1.1–25.4	0.03–29.2		
	Missing data	0	0		
Main analysis	N	34	52.6	0.84	77
	Mean (SD)	10.3 (6.7)	8.6 (8.3)		
	Min–Max	1.1–25.4	0.03–29.2		
	Missing data	0	0		
Sensitivity analysis (baseline BCVA in *MT-ND4* population)	N	34	56.1	0.83	85
	Mean (SD)	10.3 (6.7)	8.6 (8.5)		
	Min–Max	1.1–25.4	0.03–29.2		
	Missing data	0	0		
Sensitivity analysis (Lenadogene nolparvovec pool)	N	34	191.4	0.67	275
	Mean (SD)	10.3 (6.7)	9.6 (8.5)		
	Min–Max	1.1–25.4	0.03–29.4		
	Missing data	0	0		
Change from baseline BCVA at 24 months (LogMAR)*					
Naïve analysis†	N	72	96	0.78	NA
	Mean (SD)	−0.09 (0.51)	−0.14 (0.42)		
	Min–Max	–	−1.3–1.8		
	Missing data	38	0		
Main analysis	N	72	87.1	0.32	77
	Mean (SD)	−0.09 (0.51)	−0.05 (0.56)		
	Min–Max	–	−1.3–1.8		
	Missing data	38	0		
Sensitivity analysis (baseline BCVA in *MT-ND4* population)	N	72	90.6	0.50	85
	Mean (SD)	−0.09 (0.51)	−0.09 (0.53)		
	Min–Max	–	−1.3–1.8		
	Missing data	38	0		
Sensitivity analysis (Lenadogene nolparvovec pool)	N	72	308.4	0.16	275
	Mean (SD)	−0.09 (0.51)	−0.02 (0.57)		
	Min–Max	–	−1.4–1.9		
	Missing data	38	7		

Bold entries indicate p-values <0.05.
*CRR from nadir, time to initial CRR and change from baseline BCVA were calculated at eye level.
†A naïve analysis was performed, that is, a comparison between the reported absolute treatment effects from each study without adjusting for any between-trial differences, to see if the weighting method impacts the matching adjusted indirect comparison.
BCVA, best-corrected visual acuity; CRR, clinically relevant recovery; ESS, effective sample size; LogMAR, logarithm of the minimum angle of resolution; NA, not applicable.

at onset of symptoms, sex and baseline BCVA were similar between lenadogene nolparvovec and idebenone arms, while the time from vision loss to treatment (second affected eye) was statistically significantly shorter in patients treated with idebenone than in patients treated with gene therapy (4.3 (2.7) vs 8.4 (3.4) months; p<0.001) (table 3). After matching, the two

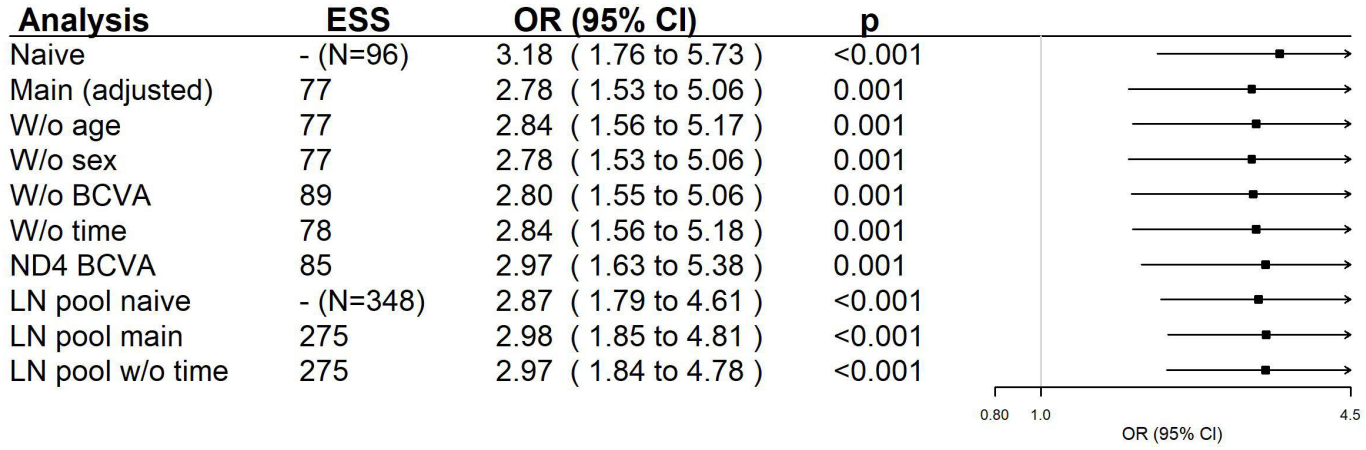


Figure 1 Matching adjusted indirect comparison (MAIC) LEROS versus REFLECT: ORs of the performed analyses. All the analyses of the MAIC comparing the clinically relevant recovery from nadir values with idebenone (LEROS) with those with lenadogene nolparvovec (REFLECT bilateral or lenadogene nolparvovec pool) are in favour of lenadogene nolparvovec, with a statistically significant difference (p≤0.001). BCVA, best-corrected visual acuity; ESS, effective sample size; LN, lenadogene nolparvovec; w/o, without. "Age" refers to age at the time of symptom onset; "BCVA" refers to the baseline value; "time" refers to the time from vision loss to treatment initiation/injection.

Table 3 Baseline characteristics of unmatched and matched populations: EAP (n=54 patients) versus REFLECT bilateral (n=48 patients)

	Idebenone patients (EAP)	Lenadogene nolparvovec patients unweighted	P value unweighted	Lenadogene nolparvovec patients weighted	P value weighted
N patients	54	48		15.9	
Age at onset of first symptoms (years)					
Mean (SD)	33.3 (17.5)	31.8 (14.4)	0.68	33.3 (16.1)	0.50
Min–Max	12.1–78.9	14.0–73.0		14.0–73.0	
Sex					
Male (%)	45 (83.0%)	37 (77.1%)	0.59	13.3 (83.6%)	1.00
Female (%)	9 (17.0%)	11 (22.9%)		2.6 (16.4%)	
Baseline BCVA (LogMAR) (best eye)*					
Mean (SD)	1.22 (0.59)	1.33 (0.41)	0.15	1.22 (0.34)	0.50
Min–Max	−0.2–1.8	0–1.8		0–1.8	
Time from vision loss to treatment injection/initiation (months) (second affected eye)†					
Mean (SD)	4.3 (2.7)	8.4 (3.4)	**<0.001**	4.3 (2.4)	0.50
Min–Max	0.4–11.4	1.7–12.0		1.7–12.0	

The baseline characteristics of EAP patients were obtained from the subgroup of patients with Leber hereditary optic neuropathy due to the *MT-ND4* variant (n=54 patients).
Bold entries indicate p-values <0.05.
*Baseline BCVA was calculated at the patient level using the best baseline BCVA among the two eyes.
†Time from vision loss to treatment was defined at the patient level as the time from the onset of symptoms in the most recently affected eye (second affected eye).
BCVA, best corrected visual acuity; EAP, expanded access programme; LogMAR, logarithm of the minimum angle of resolution.

study populations showed a reduced overlap, with an ESS of 10, that is, 33% of the original sample with the following matched baseline characteristics for both arms: mean baseline BCVA of 1.22 LogMAR and mean time from vision loss to treatment of 4.3 months (table 3).

Results of the main analysis demonstrated a numerically higher proportion of patients with CRR in REFLECT than in EAP, which did not reach statistical significance in the small sample size of 16 weighted patients (60.4% vs 39.0%; p=0.21) (CRR at patient level) (table 4). A statistically significant difference in CRR in favour of lenadogene nolparvovec was observed in the leave-one-out analyses without the covariate baseline BCVA (n=19) and time from vision loss to treatment (n=45), with an OR (95% CI) of 3.79 (1.23 to 11.69) (p=0.035) and 5.16 (2.14 to 12.46) (p<0.001), respectively (online supplemental figure 1).

Given that the mean time from vision loss to treatment for patients in the EAP study was close to that of RESCUE patients (4.3 (2.7) months[11] and 4.5 (1.4) months[14]), a post hoc sensitivity analysis was performed by matching these two populations. After matching for the four covariates, the overlap between the two populations was relevant, with an ESS of 33, that is, 92% of the original sample. This sensitivity analysis demonstrated that lenadogene nolparvovec was associated with a higher CRR rate compared with idebenone, with a statistically significant difference (69.5% vs 39.0%; p=0.011) (table 4).

The sensitivity analysis comparing the pooled lenadogene nolparvovec and EAP populations showed satisfactory overlap after matching on the four covariates, with an ESS of 63, representing 49% of the original sample. Consistent results with those of the main analysis were observed, with a statistically higher CRR rate in patients having received the gene therapy versus patients treated with idebenone (66.9% vs 39.0%, OR: 3.18 (1.56 to 6.49), p=0.002), see online supplemental figure 1 and table 4.

No statistically significant difference was observed between lenadogene nolparvovec and idebenone arms for the time to initial CRR in all analyses of the MAIC.

Table 4 Outcomes with idebenone (EAP) versus lenadogene nolparvovec (REFLECT bilateral or RESCUE or lenadogene nolparvovec pool)

		Idebenone (EAP)	Lenadogene nolparvovec	P value OR (95% CI) if applicable	ESS
CRR from nadir at 24 months*					
Naïve analysis† (EAP vs REFLECT)	N	54	48	**<0.001** 5.29 (2.22 to 12.58)	NA
	CRR	21 (39.0%)	37 (77.1%)		
	Missing data	0	0		
Main analysis (EAP vs REFLECT)	N	54	15.9	0.21 2.39 (0.76 to 7.52)	10
	CRR	21 (39.0%)	9.6 (60.4%)		
	Missing data	0	0		
Sensitivity analysis (EAP vs RESCUE)	N	54	32.5	**0.011** 3.59 (1.42 to 9.06)	33
	CRR	21 (39.0%)	22.6 (69.5%)		
	Missing data	0	3.2		
Sensitivity analysis (EAP vs lenadogene nolparvovec pool)	N	54	82.2	**0.002** 3.18 (1.56 to 6.49)	63
	CRR	21 (39.0%)	55.0 (66.9%)		
	Missing data	0	2.6		
Time to initial CRR (months)*					
Naïve analysis† (EAP vs REFLECT)	N	21	37	0.91	NA
	Mean (SD)	11.2 (7.8)	8.2 (8.3)		
	Min–Max	2.5–26.5	0.03–28.3		
	Missing data	0	0		
Main analysis (EAP vs REFLECT)	N	21	9.6	0.28	10
	Mean (SD)	11.2 (7.8)	13.0 (7.0)		
	Min–Max	2.5–26.5	0.03–28.3		
	Missing data	0	0		
Sensitivity analysis (EAP vs RESCUE)	N	21	22.6	0.77	33
	Mean (SD)	11.2 (7.8)	9.5 (7.4)		
	Min–Max	2.5–26.5	0.03–22.5		
	Missing data	0	0		
Sensitivity analysis (EAP vs lenadogene nolparvovec pool)	N	21	55.0	0.71	63
	Mean (SD)	11.2 (7.8)	10.1 (7.4)		
	Min–Max	2.5–26.5	0.03–29.4		
	Missing data	0	0		

Bold entries indicate p-values <0.05.
*CRR from nadir and time to initial CRR were calculated at patient level.
†A naïve analysis was performed, that is, a comparison between the reported absolute treatment effects from each study without adjusting for any between-trial differences, to see if the weighting method impacts the matching adjusted indirect comparison.
BCVA, best-corrected visual acuity; CRR, clinically relevant recovery; EAP, expanded access programme; ESS, effective sample size; LogMAR, logarithm of the minimum angle of resolution; NA, not applicable.

DISCUSSION

The MAIC methodology enabled the study populations to be weighed on four key covariates that may impact the response to treatment: age, sex, baseline BCVA and time from vision loss to treatment injection (lenadogene nolparvovec) or initiation (idebenone). The first MAIC comparing lenadogene nolparvovec data from REFLECT to idebenone data from LEROS demonstrated that the responder rate for CRR from nadir at 24 months was doubled for patients receiving one-time bilateral injections of lenadogene nolparvovec compared with patients treated with idebenone over 24 months.[23] The large overlap of the two weighted study populations made the results of the comparison highly relevant. Importantly, all sensitivity analyses showed comparable results to the main analysis, confirming its robustness.

In the second MAIC comparing idebenone data from the EAP with lenadogene nolparvovec data from REFLECT, there was a large reduction (~67%) in sample size due to adjustment for time from vision loss to treatment. The low overlap of the two study populations limited the value of the results of the base case model. Removing time from vision loss to treatment as a covariate in the leave-one-out analysis revealed a significantly higher CRR in favour of lenadogene nolparvovec versus idebenone (76.7% vs 39.0%; p<0.001). The post hoc sensitivity analysis comparing patients from the EAP with patients from RESCUE revealed a CRR from nadir at 24 months almost doubled with lenadogene nolparvovec compared with idebenone.[23] The results of both MAICs are therefore consistent.

Comparison of the efficacy of idebenone and lenadogene nolparvovec in the *MT-ND4* population was already conducted through a meta-analysis of CRR from nadir and final BCVA.[24] A better recovery rate was estimated with lenadogene nolparvovec than with idebenone, with 59% (54% to 64%) of eyes injected with gene therapy achieving a CRR from nadir versus 31% (24% to 40%) of eyes treated with idebenone.[24] The rates of visual recovery from nadir obtained by this method are in line with those obtained in our MAICs.

Interestingly, initial CRR in both MAICs occurred within a comparable mean time from injection of the gene therapy and initiation of the idebenone treatment (approximately 9 to 11 months), with a range in time to response comparable between the two treatment options. These results indicate that *MT-ND4*

patients treated within 12 months from vision loss achieved a clinically significant recovery on average within the first year after gene therapy injection or idebenone initiation, and, for almost all cases, within the following 24 months. Other studies have corroborated this time window for recovery with idebenone treatment.[10 25] Regarding gene therapy, other results confirm a recovery within a fixed time frame, ranging mainly from 3 to 24 months after injection of *MT-ND4* LHON patients who received similar AAV2-*ND4* gene therapies.[26 27]

For the MAIC LEROS versus REFLECT, the change from baseline of BCVA at 24 months was assessed and no statistically significant difference was observed between the two treatment arms. These results are not surprising. In LHON disease, the initial (baseline) BCVA varies considerably during the subacute phase of the disease. In lenadogene nolparvovec studies, initial BCVA ranged from LogMAR ≤0 to hand motion, including eyes with preserved BCVA, which makes the baseline value less suitable for evaluating treatment efficacy. Indeed, a proportion of lenadogene nolparvovec patients had no capacity for improvement from their baseline BCVA, explaining the overall comparable improvement with idebenone when analysed based on LogMAR change from baseline at 24 months. The nadir (lowest visual acuity), which is usually reached more than 6 months after vision loss, is a more stable and relevant reference point for assessing treatment response[2 28] and this parameter was used in the MAIC LEROS versus REFLECT.

Due to the risk of reduction in the ESS of the 48 patients bilaterally treated with gene therapy in REFLECT (96 eyes) and the inherent potential limitation of data interpretation, sensitivity analyses comparing the idebenone data from LEROS or EAP to the pooled lenadogene nolparvovec data (348 eyes) were provided. These sensitivity analyses demonstrated a statistically significant higher probability of responding to treatment with gene therapy compared with idebenone for the two MAICs ($p<0.0025$ for both base case models with a large overlap between the two study populations). This suggests that the improved efficacy of lenadogene nolparvovec over idebenone in the *MT-ND4* patients was consistent across all lenadogene nolparvovec studies, whether the injection was unilateral or bilateral.

One of the strengths of this work is the use of the MAIC, a robust statistical methodology developed and applied recently in some therapeutic areas.[21 22] Regulators have been favourable to this type of advanced statistical techniques that reduce bias when comparing clinical trial data to external comparator arms.[29] Furthermore, health technology assessment bodies have endorsed the MAIC methodology.[22 30 31] To our knowledge, these are the first MAICs comparing the effects of lenadogene nolparvovec and idebenone in the *MT-ND4* LHON population. Importantly, the similarity between the populations to be compared, which is illustrated by the large overlap after matching for the MAIC LEROS versus REFLECT and the post hoc analysis EAP versus RESCUE, makes the results of the comparisons highly relevant. Since LHON is a progressive disease, the time from disease onset to treatment injection/initiation could influence the final outcome. Therefore, to ensure comparability between the lenadogene nolparvovec and idebenone studies, only patients treated within 1 year from disease onset, which corresponds to the subacute/dynamic phase of the disease, were selected. The choice of the 24-month post-treatment time point for the outcomes was relevant for assessing the persistence of the treatment effect.

These two MAICs present some limitations. The low overlap between the EAP and REFLECT populations limits the robustness of the MAIC EAP versus REFLECT. However, as noted above, sensitivity analyses comparing EAP with RESCUE and the lenadogene nolparvovec pool revealed significant overlap and provided reliable results. The absence of ethnicity as a covariate may be a limitation. Patients from Asia carrying the *MT-ND4* variant have less severe loss of visual acuity than those from Europe and North America.[32 33] However, because of the absence of data on the number of Asian patients in EAP, and the inclusion of only one Asian patient in LEROS,[11 12] a bias related to ethnicity is unlikely. Regarding the MAIC LEROS versus REFLECT, three of the four matching covariates (age, sex and time from vision loss to treatment) were available only for the whole LHON population and not for the subgroup of interest, that is, *MT-ND4*, in the LEROS study. Nevertheless, as baseline BCVA was available in the *MT-ND4* population, we performed a sensitivity analysis using it as the only matching covariate, and the results were consistent with those of the main analysis. Some minor differences between lenadogene nolparvovec and idebenone studies in terms of LogMAR assessments may have favoured idebenone for the calculation of change in LogMAR BCVA, and lenadogene nolparvovec for the switch from off-chart to on-chart. However, sensibility analysis addressing this methodological difference yielded results consistent with those of the main analysis. It would have been more appropriate to account for the eye-level effect and within-patient correlation in the analyses, but this was not possible due to individual data from the LEROS study and EAP being unavailable. Lastly, the use of non-parametric methods for variables with a skewed distribution was not feasible due to the aggregated nature of the data from comparative studies (LEROS and EAP).

In conclusion, unanchored MAICs comparing idebenone and lenadogene nolparvovec clinical studies demonstrated a higher response rate at 24 months in *MT-ND4* patients who received a single bilateral injection of lenadogene nolparvovec compared with *MT-ND4* patients treated with a regimen of 900 mg/day of idebenone. However, to compare these two treatment options as rigorously as possible, a randomised controlled trial would be necessary. These results support lenadogene nolparvovec as a promising and effective therapeutic option for patients with LHON caused by the most common m.11778G>A mitochondrial DNA variant.

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Acknowledgements The authors are deeply grateful to all LHON patients and their families who participated in the REFLECT, RESCUE or REVERSE studies. The authors thank Anne-Coline Laurent, PharmD, PhD, who contributed to drafting the text and preparing the tables and figures. The authors acknowledge that the results

reported in this article were previously presented at the 2025 annual meetings of the European Vision & Eye Research Association (EVER), the American Academy of Ophthalmology (AAO), the Association for Research in Vision and Ophthalmology (ARVO) and the North American Neuro-Ophthalmology Society (NANOS).

Contributors Study conception and design: AP, FM and MT; methodology: AP, FM and MT; acquisition and collection of data: PY-W-M, NJN, VC, VB, AP, FM, MT and JAS; analysis and interpretation of results: AP, FM and MT; drafting of the manuscript: PYWM and MT; manuscript contributions and final approval: PYWM, NJN, VC, VB, AP, FM, MT and JAS. PYWM is the guarantor of the study.

Funding This work was funded by GenSight Biologics (no specific grant or award number applies). The funder did not influence the results of the study despite author affiliations with the funder. PYWM is supported by an Advanced Fellowship Award (NIHR301696) from the UK National Institute of Health Research (NIHR). PYWM also receives funding from the Rosetrees Trust (PGL23/100048), Fight for Sight (UK), the Isaac Newton Trust (UK), Moorfields Eye Charity (GR001376), the Addenbrooke's Charitable Trust, the National Eye Research Centre (UK), the International Foundation for Optic Nerve Disease (IFOND), the NIHR as part of the Rare Diseases Translational Research Collaboration, the NIHR Cambridge Biomedical Research Centre (NIHR203312), and the NIHR Biomedical Research Centre based at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology (NIHR203322). This research was supported by the LifeArc under grant no. 10748. LifeArc is a charity registered in England and Wales under no. 1015243 and in Scotland under no. SC037861. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. VB and NJN are supported by the National Institutes of Health's National Eye Institute core grant (P30-EY06360) (Department of Ophthalmology, Emory University School of Medicine) and by a departmental grant (Department of Ophthalmology) from Research to Prevent Blindness (New York, NY). 15 VC is supported by the Italian Ministry of Health and the Italian Ministry of Research and University through the PNRR funding system, by EU funding programmes (Horizon), by Telethon Italy and AFM-Telethon.

Competing interests PY-W-M is a consultant for GenSight Biologics, Chiesi, Stoke Therapeutics, PYC Therapeutics and Neurophth Therapeutics; he has received research support from GenSight Biologics and Santhera Pharmaceuticals. NJN is a consultant for GenSight Biologics, Chiesi, Stoke Therapeutics, Neurophth Therapeutics and Eli Lilly; has received research support from GenSight Biologics. VC is a consultant for GenSight Biologics, Chiesi and Pretzel Therapeutics. VB is a consultant for GenSight Biologics, Chiesi and Topcon Medical. AP has no conflict of interest. FM is a consultant for AbbVie, Arcagy, Artic, Biocodex, Bioprojet, Brenus, Carely, Ceremast, Ceva, Cureety, DBV Technologies, Emercell, Eurofins Optimed, Fort, IFM, IJL, Imcheck, Mapreg, Monitoring Force, Onward, Orphelia, Ose, Pfizer, PTC, Pulsesight, Recordati, Remind, Sparing Vision, Spine Vision, Takeda, Unicancer and Urgo; is a member of a data safety monitoring board or advisory board at Servier. MT is an employee of GenSight Biologics. JAS is a consultant for Avista Therapeutics, Essilor Luxottica and Lightstone Ventures; is owner/co-owner/founder/co-founder and has personal financial interests (stock/stock options) in Gensight Biologics, Sparing Vision, Prophesee, Tilak Healthcare, Avista, Tenpoint, SharpEye, Cilensee and Netramind; is a member of the scientific advisory board of Gilbert Foundation, Foundation Fighting Blindness and Institute of Ophthalmology Basel; Is an observer at Sparing Vision and Avista; is president of Fondation Voir et Entendre and StreetLab; is director of GenSight Biologics; is executive Vice-President of UPMC Enterprises; has patents for allotopic expression, Rod-Derived Cone Viability Factor and related patents; is a recipient for patent royalties and GenSight Biologics.

Patient consent for publication Not applicable.

Ethics approval The REFLECT clinical study used for matching indirect comparisons was approved by an ethics committee or institutional board at all centres: Belgium, Universitair Ziekenhuis Gent (2018/0074); France, Comité de Protection des Personnes Nord-Ouest II (2018/15); Italy, 16 Comitato Etico Interaziendale Bologna-Imola - CEBI (88929/13/07/2018); Spain, CEIC Hospital Universitario Ramon y Cajal (18.01.1161-GHM); Taiwan, Taipei Veterans General Hospital, Institutional Review Board (2018-03-002A); UK, NRES Committee - London West London & GTAC (18/LO/0521); USA, Wills Eye Hospital IRB (15.1118), Emory University-EC (IRB00100950), UCLA Medical Center IRB (18-000742), WIRB (20180153), Human Studies Committee (18-051H), Mount Sinai School of Medicine (IBC-2018-041) and Vanderbuilt IRB (180255).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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