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Five-Year Outcomes of Lenadogene Nolparvovec Gene Therapy in Leber Hereditary Optic Neuropathy

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Supplemental content

IMPORTANCE Limited studies have assessed the long-term benefit/risk of gene therapy for Leber hereditary optic neuropathy (LHON).

OBJECTIVE To determine the safety and efficacy of lenadogene nolparvovec in patients with LHON due to the *MT-ND4* gene variant for up to 5 years after administration.

DESIGN, SETTING, AND PARTICIPANTS The RESCUE and REVERSE Long-Term Follow-up Study (RESTORE), conducted from 2018 to 2022, is the 5-year follow-up study of the 2 phase 3 clinical studies RESCUE (Efficacy Study of Lenadogene Nolparvovec for the Treatment of Vision Loss Up to 6 Months From Onset in LHON Due to the *MT-ND4* Mutation) and REVERSE (Efficacy Study of Lenadogene Nolparvovec for the Treatment of Vision Loss From 7 Months to 1 Year From Onset in LHON Due to the *MT-ND4* Mutation). At the end of each study, ie, 2 years after gene therapy administration, patients were offered enrollment in the RESTORE trial, a multinational, multicenter, prospective study, for an additional 3 years of follow-up. Patients with LHON due to the *MT-ND4* gene variant received lenadogene nolparvovec in 1 eye and a sham injection in the other eye.

INTERVENTION Lenadogene nolparvovec was administered as a single intravitreal injection in the RESCUE/REVERSE studies.

MAIN OUTCOMES AND MEASURES Measures included best-corrected visual acuity (BCVA), quality of life using the National Eye Institute visual functioning questionnaire 25 (NEI VFQ-25), and adverse events.

RESULTS Among the 76 patients who received gene therapy in the RESCUE (n = 39) and REVERSE (n = 37) studies, 72 (94.7%) completed these studies; 62 patients (81.6%) participated in the RESTORE trial, and 55 patients (72.4%) completed the 5-year follow-up. Participants were mostly male (49 [79.0%]) with a mean (SD) age of 35.9 (15.3) years at treatment. At baseline, the mean (SD) BCVA was 1.5 (0.5) logMAR (20/600 Snellen) in eyes to be treated with lenadogene nolparvovec and 1.4 (0.5) logMAR (20/500) in sham eyes. At the end of the RESCUE/REVERSE trials, ie, 2 years after treatment, eyes treated with lenadogene nolparvovec and eyes treated with sham reached a mean BCVA value of 1.4 (0.6) logMAR (20/500). The mean (SD) change from baseline to year 2 was −0.05 (0.6) logMAR (+1 line) and 0.01 (0.6) logMAR (−0 line) in gene therapy–treated and sham eyes, respectively (difference, −0.03; 95% CI, −0.16 to 0.09; P = .60). Five years after treatment, the bilateral improvement from nadir was similar to that observed at 2 years, with a mean (SD) change in BCVA of −0.4 (0.5) logMAR (more than +4 lines) for eyes treated with lenadogene nolparvovec and −0.4 (0.4) logMAR (+4 lines) for eyes treated with sham (difference, −0.05; 95% CI, −0.15 to 0.04; P = .27). An improvement of at least −0.3 logMAR (+3 lines) from the nadir in at least 1 eye was observed in 66.1% of participants (41 of 62). Between 2 and 5 years, intraocular inflammation was noted in 4 participants with 8 events in eyes treated with lenadogene nolparvovec and 1 event in an eye treated with sham.

CONCLUSIONS AND RELEVANCE In this analysis of the RESTORE trial, follow-up of patients with LHON due to the *MT-ND4* gene variant unilaterally treated with lenadogene nolparvovec demonstrated a sustained bilateral improvement in BCVA and a good safety profile up to 5 years after treatment. This evidence of persistent benefit over time is promising for the use of gene therapy in these patients.

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The m.11778G>A variant of the *MT-ND4* gene is the most common cause of Leber hereditary optic neuropathy (LHON), a mitochondrial genetic disease that preferentially affects retinal ganglion cells.[1] Patients with LHON present with severe bilateral sequential vision loss, significantly impacting their quality of life (QoL).[1,2]

Lenadogene nolparvovec (rAAV2/2-ND4 or Lumevoq [GenSight Biologics SA]) is an adenoassociated virus (AAV)-based ocular gene therapy, developed to treat patients carrying the m.11778G>A mitochondrial DNA gene variant. Its efficacy and safety have been evaluated in 4 clinical studies showing an improvement in best-corrected visual acuity (BCVA) up to 2 years after administration and a good safety profile.[3-6]

The RESCUE and REVERSE Long-Term Follow-up Study (RESTORE) is the follow-up study of the 2 phase 3 clinical studies, RESCUE (Efficacy Study of Lenadogene Nolparvovec for the Treatment of Vision Loss Up to 6 Months From Onset in LHON Due to the *MT-ND4* Mutation)[4] and REVERSE (Efficacy Study of Lenadogene Nolparvovec for the Treatment of Vision Loss From 7 Months to 1 Year From Onset in LHON Due to the *MT-ND4* Mutation),[5] designed to determine the 5-year safety and efficacy of lenadogene nolparvovec.[7]

Key Points

Question What are the 5-year outcomes of lenadogene nolparvovec gene therapy in patients with Leber hereditary optic neuropathy (LHON) due to the *MT-ND4* gene variant?

Findings In the RESCUE and REVERSE Long-Term Follow-up Study (RESTORE) including 62 patients, sustained bilateral improvement in visual acuity with improved quality of life and good overall tolerability were observed up to 5 years after unilateral lenadogene nolparvovec intravitreal administration in patients with LHON due to the *MT-ND4* gene variant.

Meaning These results demonstrate the persistent benefit over time from a single dose of lenadogene nolparvovec, which is promising for the use of gene therapy in LHON due to the *MT-ND4* gene variant.

Methods

Ethics

The RESTORE study was initiated in January 2018 (first patient included), and the statistical analysis plan was completed in June 2022, before database lock on July 4, 2022. The study protocol and its amendment were reviewed and approved by an institutional review board (IRB) or ethics committee (South Central-Oxford A Research Ethics Committee, Bristol, UK; Emory University IRB, Atlanta, Georgia, University of California Los Angeles General Campus IRB, Los Angeles, California, and Wills Eye Hospital IRB, Philadelphia, Pennsylvania; Comité de Protection des Personnes Sud-Est III, Bron, France; Comitato Etico di Area Vasta Emilia Centro della Regione, Bologna, Italy; Ethikkommission der Medizinischen Fakultät der Ludwig Maximilians Universität München, München, Germany). Trial protocol versions 1 and 2 are available in Supplement 1 and Supplement 2, and the statistical analysis plan is available in Supplement 3. All patients provided written informed consent before inclusion and did not receive a stipend or other form of compensation for participating.

Patients' unmasking was permitted at the time of database lock of the RESCUE and REVERSE trials. The treatment assigned to each eye was not systematically communicated to the participants and the site medical teams, but the details were known by the sponsor study team. Investigators received the information of the primary end point results at 48 weeks after lenadogene nolparvovec injection in the RESCUE and REVERSE studies once the main analysis had been completed. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Study Participants

Patients with LHON due to the *MT-ND4* gene variant were previously treated with lenadogene nolparvovec in the RESCUE[4] or REVERSE[5] study. Lenadogene nolparvovec had been administered as a single intravitreal injection at a dose of 9×10^{10} viral genomes; the other eye had received a sham injection. RESCUE trial participants were treated within 6 months after vision loss, and REVERSE trial participants were treated between 6 and 12 months after vision loss. At the end of each study (2 years after administration), patients were offered enrollment in the RESTORE trial for an additional 3 years of follow-up. Interim results have been described by Biousse and colleagues.[7] Race and ethnicity data were not collected in the REVERSE, RESCUE, and RESTORE trials as most regulatory bodies do not allow the collection of this information.

Outcome Measures

In the RESTORE study, all BCVA values were converted into logMAR. The Snellen and Early Treatment Diabetic Retinopathy Study (ETDRS) lines/letters equivalents are reported in this publication.

The predefined responder criteria were an improvement of at least −0.2 logMAR (+2 lines; +10 ETDRS letters) or −0.3 logMAR (+3 lines; +15 ETDRS letters) from nadir, a clinically relevant recovery (an improvement of at least 0.2 logMAR for eyes on-chart at nadir, and eyes that converted to on-chart for eyes that were off-chart at nadir), a clinically relevant stabilization (logMAR <+1.0 [<20/200 Snellen] at baseline in at least 1 eye that was maintained in this eye), and a clinically relevant benefit (defined as either clinically relevant stabilization, clinically relevant recovery from nadir, or both). The nadir was defined as the worst BCVA value from baseline to the time of the final assessment; it could be before (at baseline) or after treatment. Since the nadir will be the worst BCVA across multiple BCVA tests, it could be 1 low BCVA 1 time due to poor effort or fixation, especially when measuring BCVA at these relatively poor levels of vision, such as a Snellen equivalent of 20/800. Therefore, it is possible with this method that BCVA improvements could be regression to the mean, that is, the BCVA improved from 1 BCVA obtained at 1 time, which was low due to poor effort or fixation.

QoL was measured using the National Eye Institute Visual Functioning Questionnaire 25 (NEI VFQ-25).[8] A change from baseline of 4 or more points was considered a clinically meaningful improvement.[9]

Systemic adverse events (AEs) related to treatment or intravitreal injection and all ocular AEs were recorded. AEs of special interest (AESI) included intraocular inflammation and elevation of intraocular pressure (IOP).

Statistical Analysis

Analyses were conducted using SAS software, version 9.4 or higher (SAS Institute). LogMAR values are presented as observed or imputed data; missing values were imputed by last observed carried forward. The difference in mean change from baseline or nadir (least square means) in BCVA between the 2 treatment groups, with its 95% CI and *P* value, was estimated using a multivariate analysis of covariance model with baseline or nadir value and eye status as covariates and a random intercept for patient. Logistic regression and generalized estimating equation models were used for patient-responder end points and eye-responder end points, respectively.

The evolution of BCVA over time was represented using a locally estimated scatterplot smoothing (LOESS), nonparametric, local regression model in which each patient's eyes were considered independently. LOESS curves with 95% CI were presented from 12 months up to 86 months after vision loss (longest follow-up in the RESTORE study). The same LOESS model was applied to a pool of 11 natural history studies of LHON due to the *MT-ND4* gene variant, as described previously.[10,11] This additional analysis was defined in a specific statistical analysis plan. No multiplicity adjustment was applied. All *P* values were 2-sided, and $P < .05$ was considered statistically significant.

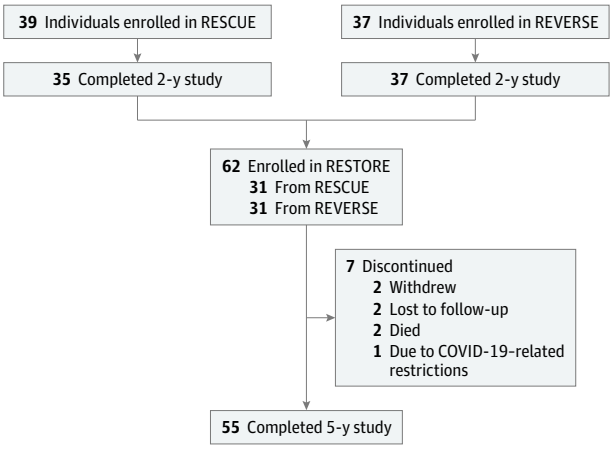
Results

Study Participants

Among the 76 patients with LHON due to the *MT-ND4* gene variant who received gene therapy in the RESCUE (n = 39) and REVERSE (n = 37) studies, 72 (94.7%) completed these studies. A total of 62 patients (81.6%) participated in the RESTORE trial, and 55 patients (72.4%) completed the 5-year follow-up (**Figure 1**). Of the 7 participants who discontinued before the end of the study, 2 patients withdrew their consent, 2 were lost to follow-up, 2 died, and 1 did not want to visit the study site because of the COVID-19 pandemic. In the RESTORE study, 49 participants were male (79.0%), 13 were female (21.0%), and the mean (SD) age at the time of treatment administration was 35.9 (15.3) years, with 7 participants aged 15 to 18 years.

The relevant clinical characteristics of the 14 patients who were not included in the RESTORE study are displayed in eTable 1 in Supplement 4. Overall, no differences in demographics and BCVA values at the end of the RESCUE and REVERSE trials were observed between the 14 patients who did not participate in the RESTORE study and the 62 patients who were included.

Figure 1. Flowchart of the Participants in RESCUE (Efficacy Study of Lenadogene Nolparvovec for the Treatment of Vision Loss Up to 6 Months From Onset in LHON Due to the *MT-ND4* Mutation), REVERSE (Efficacy Study of Lenadogene Nolparvovec for the Treatment of Vision Loss From 7 Months to 1 Year From Onset in LHON Due to the *MT-ND4* Mutation), and the RESCUE and REVERSE Long-Term Follow-up Study (RESTORE) Studies



BCVA and QoL

At baseline, ie, at the start of the RESCUE and REVERSE trials, eyes to be treated with lenadogene nolparvovec had a mean (SD) BCVA of 1.5 (0.5) logMAR (20/600 Snellen), and sham eyes showed a mean (SD) BCVA of 1.4 (0.5) logMAR (20/500 Snellen) (eTable 2 in Supplement 4). BCVA values at baseline were lower, meaning better, in RESCUE participants than in REVERSE participants (eTable 3 in Supplement 4). Overall, at the end of the RESCUE and REVERSE trials, ie, 2 years after treatment, eyes treated with lenadogene nolparvovec and eyes treated with sham reached a mean (SD) BCVA value of 1.4 (0.6) logMAR (20/500). The mean (SD) change from baseline to year 2 was −0.05 (0.6) logMAR (+1 line; +3 letters) for eyes treated with gene therapy and 0.01 (0.6) logMAR (0 line; −1 letter) for eyes that received a sham injection (difference, −0.03; 95% CI, −0.16 to 0.09; $P = .60$). When looking at the change from nadir, considered as a most relevant assessment for a disease such as LHON, at year 2, the mean (SD) change was −0.4 (0.4) logMAR (+4 lines; +20 letters) in eyes treated with lenadogene nolparvovec and −0.3 (0.3) logMAR (+3 lines; +17 letters) in eyes treated with sham injection (eTable 2 in Supplement 4). At year 5, the mean (SD) improvement in BCVA from nadir reached −0.4 (0.5) logMAR (+4 lines; +22 letters) in eyes treated with lenadogene nolparvovec and −0.4 (0.4) logMAR in eyes treated with sham (+4 lines; +20 letters; difference, −0.05; 95% CI, −0.15 to 0.04; $P = .27$) (eTable 2 in Supplement 4). Analyses using observed data showed similar results (**Table 1**). Eyes treated with lenadogene nolparvovec and those treated with sham of the RESCUE participants showed a mean (SD) change in BCVA from nadir of −0.5 (0.4) logMAR (+4 lines; +23 letters) and −0.4 (0.4) logMAR (+4 lines; +21 letters), whereas for REVERSE participants, BCVA improved from nadir by −0.4 (0.4) logMAR (+3 lines; +18 letters) in eyes receiving lenadogene nolparvovec and −0.4 (0.3) logMAR (+4 lines; +19 letters) in eyes receiving sham (eTable 3 in Supplement 4).

Table 1. Best-Corrected Visual Acuity (BCVA) Values, Change in BCVA and Responder Analyses, Observed Data[a]

Variable	Lenadogene nolparvovec-treated eyes	Sham-treated eyes	Difference between groups (95% CI)	*P* value
Baseline				
No.	62	62	NA	NA
Mean (SD)	1.5 (0.5) 20/600 Snellen	1.4 (0.5) 20/500 Snellen		
Min-max	−0.10 to 2.30	−0.20 to 2.00		
Year 2				
No.	62	61	NA	NA
Mean (SD)	1.4 (0.6) 20/500 Snellen	1.4 (0.6) 20/500 Snellen		
Min-max	−0.20 to 4.00	−0.20 to 4.00		
Year 5				
No.	51	51	NA	NA
Mean (SD)	1.4 (0.7) 20/500 Snellen	1.3 (0.5) 20/400 Snellen		
Min-max	−0.20 to 4.50	−0.20 to 2.30		
Change from baseline to year 2				
No.	62	61	−0.04 (−0.16 to 0.09)[b]	.58
Mean (SD)	−0.05 (0.6) +1 line (+3 ETDRS letters)	0.01 (0.6) −0 line (−1 ETDRS letter)		
Min-max	−1.30 to 3.00	−0.80 to 2.50		
Change from baseline to year 5				
No.	51	51	0.06 (−0.08 to 0.20)[b]	.42
Mean (SD)	−0.1 (0.7) +1 line (+5 ETDRS letters)	−0.1 (0.4) +1 line (+6 ETDRS letters)		
Min-max	−1.40 to 3.50	−1.20 to 1.70		
Change from nadir to year 2[c]				
No.	62	61	−0.05 (−0.14 to 0.04)[b]	.23
Mean (SD)	−0.4 (0.4) +4 lines (+20 ETDRS letters)	−0.3 (0.3) +3 lines (+17 ETDRS letters)		
Min-max	−2.40 to 0.00	−1.20 to 0.00		
Change from nadir to year 5[c]				
No.	51	51	0 (−0.08 to 0.08)[b]	.99
Mean (SD)	−0.4 (0.4) +4 lines (+21 ETDRS letters)	−0.4 (0.4) +4 lines (+20 ETDRS letters)		
Min-max	−1.40 to 0.00	−1.60 to 0.00		
≤-0.3 LogMAR from nadir, No./total No. (%)				
Year 5	31/51 (60.8)	29/51 (56.9)	3.92 (−15.17 to 23.01)	NA
≤-0.2 LogMAR from nadir, No./total No. (%)				
Year 5	35/51 (68.6)	39/51 (76.5)	7.84 (−9.41 to 25.10)	NA
Clinically relevant recovery from nadir, No./total No. (%)[d]				
Year 5	30/62 (48.4)	35/62 (56.5)	8.07 (−9.46 to 25.59)	NA
Clinically relevant stabilization, No./total No. (%)[e]				
Year 5	7/9 (77.8)	7/10 (70.0)	7.78 (−31.52 to 47.08)	NA
Clinically relevant benefit, No./total No. (%)[f]				
Year 5	30/62 (48.4)	36/62 (58.1)	9.68 (−7.80 to 27.16)	NA
≤1.6 LogMAR [on-chart], No./total No. (%)				
Year 5	39/51 (76.5)	42/51 (82.4)	5.88 (−9.77 to 21.54)	NA

Abbreviations: CRB, clinically relevant benefit; CRR, clinically relevant recovery; CRS, clinically relevant stabilization; ETDRS, Early Treatment Diabetic Retinopathy Study; NA, not applicable.

[a] Data were analyzed as observed data. Lowercase *n* represents the number of eyes. A line corresponds to 5 letters and is considered read for at least 3 letters read. In a conservative approach, the improvement of the last line corresponds to an improvement of 4 or 5 letters. As an example, 18 letters improvement corresponds to 3 lines improvement and 19 letters improvement corresponds to 4 lines improvement.

[b] Multivariate model with baseline or nadir value and eye status as covariates and random intercept for patient.

[c] The nadir was defined for each eye of each patient as the worst BCVA value observed from baseline to the time point of interest. As a result, the nadir value could change depending on the period of interest.

[d] Clinically relevant recovery was defined as a BCVA assessment improving from >1.6 logMAR (>20/800) at nadir to ≤1.6 logMAR (≤20/800), or an improvement ≥−0.2 logMAR (+2 lines on the ETDRS chart) if value at nadir was ≤1.6 logMAR (≤20/800), ie, no letters read on the ETDRS chart at 1 m. All available observed data are used with no imputation.

[e] Clinically relevant stabilization was defined as logMAR <+1.0 (<20/200) at baseline in at least 1 eye that was maintained in this eye. All available observed data are used with no imputation.

[f] Clinically relevant benefit was defined as either clinically relevant stabilization, clinically relevant recovery from nadir, or both.

Five years after treatment, an improvement of at least −0.2 logMAR (+2 lines) and −0.3 logMAR (+3 lines) from nadir in at least 1 eye was observed in 79.0% of participants (49 of 62) and 66.1% of participants (41 of 62), respectively (eTable 2 in Supplement 4). Based on the clinically relevant recovery from nadir, the responder rate was 71.0% (44 of 62). In total, 80.6% of participants (50 of 62) of participants had their BCVA in at least 1 eye on-chart at year 5. At baseline, 13 of 62 participants (21.0%) had at least 1 eye with logMAR <1 (<20/200); at year 5, 10 of 13 participants (76.9%) had clinically relevant stabilization. In total, 71.0% of participants (44 of 62) had a clinically relevant benefit at year 5 (eTable 2 in Supplement 4). Changes in BCVA and responder analyses by gender are presented in eTable 4 in Supplement 4. Overall, change in BCVA from nadir and the rates of responders at year 5 were similar in female (n = 13) and male (n = 49) participants (eTable 4 in Supplement 4).

For participants in the REVERSE, RESCUE, and RESTORE trials (n = 76), the evolution of BCVA over time, represented by the LOESS curve, showed an improvement in both eyes from month 12 up to the last available value (86 months post vision loss) (**Figure 2**). Of note, the curve starts at 12 months after onset when 92.7% of eyes (141 of 152) in the RESCUE and REVERSE trials had received treatment. For the natural history pool, the LOESS curve showed a decline of BCVA over time. Analysis at the last available observation showed a statistically significant better BCVA in the treated pool vs the natural history pool, with a clinically relevant mean difference of −0.32 (95% CI, −0.44 to −0.21) logMAR (+3 lines) in favor of patients receiving lenadogene nolparvovec (P <.001) and no overlap of the 95% CI.

The improvement in BCVA was greater and more frequent from baseline to year 2, and from baseline to year 5, than the improvement from year 2 to year 5 (eFigure 1 in Supplement 4). The pattern of BCVA improvement was similar for eyes treated with lenadogene nolparvovec and eyes that received a sham injection, in terms of individual data (eFigure 1 in Supplement 4) and mean change (eFigure 2 in Supplement 4). Kaplan-Meier analysis for time to improvement of at least 0.3 logMAR (≥+3 lines) from baseline to year 5 is shown in eTable 5 and eFigure 3 in Supplement 4.

Clinically significant improvement from baseline was observed in 7 of 10 subscale scores of the NEI VFQ-25 questionnaire at 5 years (**Table 2**).[9] The composite score showed a mean gain from baseline of 7 points. In RESCUE trial participants, the composite score improved by 3 points from baseline, whereas in REVERSE trial participants, it improved by 10 points (eTable 6 in Supplement 4).

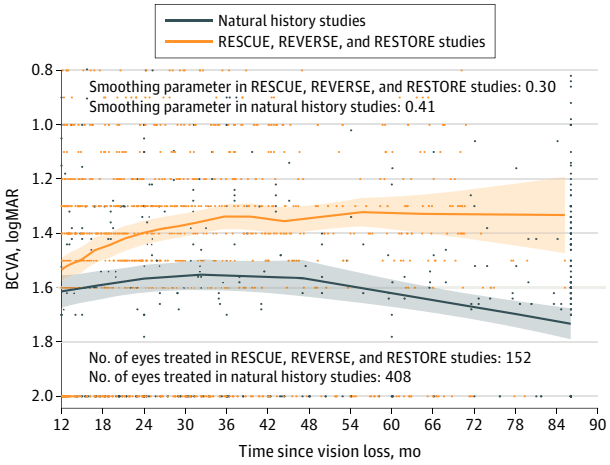
Safety

During the RESTORE study, no systemic AEs related to the study treatment or procedure were reported. Two participants died, one from cardiovascular disease and the other from glioblastoma; these events were not related to the study treatment or procedure, and no vector DNA was found in the brain biopsy of the participant's glioblastoma.[12]

A total of 36 ocular AEs occurred in 24 eyes receiving lenadogene nolparvovec (38.7%), and 21 ocular AEs were reported in 18 eyes receiving sham (29.0%). Ocular AEs mainly included cataract (6 participants), intraocular inflammation (8 events in lenadogene nolparvovec eyes and 1 in a sham eye; 4 participants), and increases in IOP (3 events in lenadogene nolparvovec eyes and 2 in sham eyes; 4 participants) (eTable 7 in Supplement 4). Regarding the patient who presented with intraocular inflammation (mild anterior uveitis) in the sham eye, it should be noted that the other eye, injected with the gene therapy, also developed a mild anterior and intermediate uveitis. Most ocular events (48 of 57 [84%]) were mild, none were severe or serious, and none led to study discontinuation. All intraocular inflammation events occurred in the anterior chamber or vitreous) (eTable 7 in Supplement 4).

Overall, intraocular inflammation and elevation of IOP occurred with a higher incidence between baseline and year 2 (in the RESCUE or REVERSE trials) than between year 2 and year 5 (in the RESTORE trial) and tended to be shorter after 2 years of treatment. From baseline to year 2, the rate of intraocular inflammation was 79.0% in eyes (49 of 62) treated with gene therapy vs 10.9% in eyes (5 of 62) treated with sham, whereas between year 2 and year 5, this rate was 16.7% in eyes (4 of 62) treated with gene therapy and 5.6% in eyes (1 of 62) treated with sham (eTable 7 in Supplement 4). The intensity of these AESI was similar irrespective of the time period. **Table 3** shows the characteristics of intraocular inflammation and elevation of IOP over 5 years by initial study. The rate of intraocular inflammation was similar in RESCUE and REVERSE patients in eyes treated with lenadogene nolparvovec (71.0% [22 of 31] and 87.1% [27 of 31], respectively) and in eyes treated with sham (9.7% [3 of 31] for both studies). Regardless of the initial study, the characteristics of ocular inflammation and elevation of IOP were similar in patients treated with gene therapy (Table 3).

Figure 2. Evolution of Best-Corrected Visual Acuity (BCVA) in Eyes (Treated and Sham) From the REVERSE (Efficacy Study of Lenadogene Nolparvovec for the Treatment of Vision Loss From 7 Months to 1 Year From Onset in LHON Due to the *MT-ND4* Mutation), RESCUE (Efficacy Study of Lenadogene Nolparvovec for the Treatment of Vision Loss Up to 6 Months From Onset in LHON Due to the *MT-ND4* Mutation), and the RESCUE and REVERSE Long-Term Follow-up Study (RESTORE) studies vs Natural History Eyes



The evolution of BCVA over time for treated eyes (n = 76 [RESCUE n = 39; REVERSE n = 37]) and natural history eyes (n = 408) was estimated by locally estimated scatterplot (LOESS) regression (solid line) with 95% CI around the fitted curve (shaded area). For natural history eyes, BCVA values after 86 months were assigned to the 86-month time point using the next observation carried backward method. Smoothing parameter: 0.302 for treated eyes and 0.413 for natural history eyes. The statistically significant difference between treated eyes (lenadogene nolparvovec and sham) and natural history eyes is illustrated by the nonoverlapping CIs of LOESS curves. Mean difference at last observation was estimated by a mixed-model analysis of covariance with repeated measures: −0.32 (95% CI, −0.44 to −0.21) logMAR (P <.001 vs natural history and Kruskal-Wallis test: P <.001 vs natural history).

Discussion

In the RESCUE, REVERSE, and RESTORE trials, the change in BCVA from nadir was judged to be more relevant than the

Table 2. National Eye Institute Visual Functioning Questionnaire 25 (NEI VFQ-25)[a]

	Baseline		Year 2		Year 5		Change from baseline to year 2		Change from baseline to year 5		Change from year 2 to year 5	
NEI VFQ-25 subscale scores	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD) [95% CI]	No.	Mean (SD) [95% CI]	No.	Mean (SD) [95% CI]
Mental health score	62	29.5 (21.7)	62	45.8 (26.6)	51	51.0 (25.7)	62	16.2 (21.7) [10.72 to 21.74]	51	22.2 (25.9) [14.89 to 29.47]	51	4.3 (21.6) [−1.78 to 10.36]
Role difficulties score	62	32.1 (26.7)	62	44.3 (28.6)	51	48.5 (28.4)	62	12.3 (32.1) [4.16 to 20.44]	51	17.2 (29.2) [8.96 to 25.36]	51	3.9 (29.1) [−4.26 to 12.11]
Dependency score	62	32.0 (25.9)	62	44.8 (29.0)	51	45.3 (28.4)	62	12.8 (34.4) [4.04 to 21.50]	51	14.1 (32.9) [4.79 to 23.32]	51	−0.3 (20.9) [−6.20 to 5.55]
Near activities score	62	27.0 (20.3)	62	33.6 (24.3)	51	39.2 (22.7)	62	6.6 (28.2) [−0.57 to 13.75]	51	12.8 (26.4) [5.31 to 20.18]	51	3.6 (19.7) [−1.94 to 9.13]
General vision score	61	34.4 (16.4)	62	39.4 (20.2)	51	41.6 (21.5)	61	5.3 (21.9) [−0.36 to 10.85]	50	7.6 (22.5) [1.22 to 13.98]	51	1.2 (16.2) [−3.38 to 5.73]
Distance activities score	62	38.2 (20.8)	62	42.5 (23.5)	51	44.1 (23.9)	62	4.2 (24.4) [−1.95 to 10.42]	51	6.9 (25.1) [−0.12 to 14.01]	51	−0.3 (16.7) [−5.01 to 4.36]
Social functioning score	62	47.2 (25.4)	62	49.0 (24.3)	51	51.7 (25.5)	62	1.8 (31.4) [−6.17 to 9.80]	51	4.4 (31.5) [−4.45 to 13.27]	51	0.3 (20.8) [−5.62 to 6.11]
Peripheral vision score	62	61.7 (26.7)	62	62.1 (26.3)	51	61.8 (25.2)	62	0.4 (33.7) [−8.16 to 8.97]	51	1.0 (30.4) [−7.57 to 9.53]	51	−3.4 (27.4) [−11.14 to 4.27]
Color vision score	62	72.6 (28.5)	62	67.3 (30.6)	51	68.6 (27.3)	62	−5.2 (33.9) [−13.86 to 3.37]	51	−2.5 (36.8) [−12.81 to 7.91]	51	−0.5 (23.7) [−7.16 to 6.18]
Ocular pain score	62	88.1 (17.9)	62	85.5 (20.3)	51	85.5 (20.2)	62	−2.6 (17.8) [−7.15 to 1.91]	51	−2.9 (21.6) [−9.01 to 3.13]	51	−0.5 (14.4) [−4.53 to 3.55]
Composite score[b]	62	43.6 (16.7)	62	48.0 (19.2)	51	50.0 (17.8)	62	4.4 (20.1) [−0.73 to 9.48]	51	7.0 (19.1) [1.63 to 12.37]	51	0.5 (10.9) [−2.57 to 3.54]

Abbreviations: No., number of patients; NEI VFQ-25, National Eye Institute visual functioning questionnaire-25.

[a] The results of the general health rating question were excluded because of a high level of missing data and the driving score was not presented because it is not relevant to the population of individuals with Leber hereditary optic neuropathy.

[b] The composite score is an unweighted average of the responses to all list items except for the general health rating question.[8] A change from baseline ≥4 points is considered a clinically meaningful improvement.[9]

change from baseline for assessing eye response. During the subacute phase of LHON, BCVA deteriorates rapidly, shifting from on- to off-chart values over a few weeks or months.[13] In other words, baseline BCVA varies greatly depending on the stage of the disease at the time of patient enrollment, which makes it an unsuitable reference point for a meaningful comparison between study and even within study. Baseline BCVA values for RESTORE participants clearly illustrate the inhomogeneity of VA in the first year of LHON disease, showing differences between RESCUE and REVERSE participants, with better BCVA values for RESCUE participants, consistent with the early stage of their disease. Similarly, the pooled study population shows a wide dispersion of the baseline BCVA values from logMAR −0.2 (not yet affected second eyes from the RESCUE trial) to the worst value of +2.3. In contrast, once the nadir BCVA has been reached, it shows relatively little variation over time.[14] Therefore, the nadir is a more stable and relevant reference value for assessing the treatment effect and has been defined as the worst VA measurement of each eye of each patient with LHON from baseline to the time point of interest, documented in multiple publications and endorsed by LHON clinical experts.[14-16]

A bilateral improvement in BCVA had been reported in patients with LHON due to the *MT-ND4* gene variant unilaterally injected with lenadogene nolparvovec at the end of the RESCUE and REVERSE studies and maintained up to 5 years after treatment in the RESTORE study.[4,5] This contralateral effect of lenadogene nolparvovec in the contralateral untreated eyes has been consistently demonstrated in all 5 clinical studies (REVEAL [Safety and Tolerability Study of Lenadogene Nolparvovec in Patients With LHON Due to Mutations in *MT-ND4*], RESCUE, REVERSE, RESTORE, and REFLECT [Efficacy and Safety Study of Bilateral Intravitreal Injection of Lenadogene Nolparvovec in LHON Subjects Due to the *MT-ND4* Mutation for Up to 1 Year]).[3-7] As in the 5 years' data of the RESCUE, REVERSE, and RESTORE trials, this phenomenon has been observed in the REVEAL and REFLECT studies in untreated and placebo eyes, respectively.[3,6] In an effort to explore the potential mechanisms contributing to such an effect, nonclinical investigations were conducted and showed the following: (1) lenadogene nolparvovec (viral vector DNA) was able to transfer from injected eyes to uninjected eyes of healthy monkeys,[17] and (2) the transcription product of lenadogene nolparvovec (mRNA transgene) was expressed in the contralateral eyes after unilateral injection in a mouse model of glaucoma.[18] Importantly, postmortem studies of 2 RESCUE patients who received lenadogene nolparvovec intravitreal injection in 1 eye and a sham injection in the other provided eye autopsy data at 15 months and 6.5 years after treatment. In both patients, the AAV2-*ND4* transgene was found in the retinas of both eyes, the injected eye and the sham eye. These results provide the first evidence of successful gene transduction of retinal ganglion cells, occurring in both eyes of 2 patients with LHON due to the *MT-ND4* gene variant after unilateral injection of lenadogene nolparvovec.[19] It is worth noting that bilateral improvement after unilateral treatment has also been shown in LHON due to the *MT-ND4* gene variant with other AAV-based gene therapy products. Two independent research groups (Guy group, Bascom Palmer Eye Institute, Miami, Florida,

Table 3. Intraocular Inflammation and Elevation of Intraocular Pressure (IOP) by Initial Study Over 5 Years

Variable	RESCUE		REVERSE		Pooled	
	Lenadogene nolparvovec-treated eyes (n = 31)	Sham-treated eyes (n = 31)	Lenadogene nolparvovec-treated eyes (n = 31)	Sham-treated eyes (n = 31)	Lenadogene nolparvovec-treated eyes (n = 62)	Sham-treated eyes (n = 62)
Eyes with at least 1 intraocular inflammation AESI, No. (%)	22 (71.0)	3 (9.7)	27 (87.1)	3 (9.7)	49 (79.0)	6 (9.7)
No. of intraocular inflammation events	59	3	65	3	124	6
Duration, d						
No.	57	3	65	3	122	6
Mean (SD)	214.1 (235.6)	54.7 (16.2)	307.2 (380.7)	355.7 (270.0)	263.7 (323.3)	205.2 (237.6)
Median (IQR) [range]	142.00 (61.00 to 294.00) [7.00 to 1063.00]	64.00 (36.00 to 64.00) [36.00 to 64.00]	107.00 (35.00 to 504.00) [1.00 to 1856.00]	504.00 (44.00 to 519.00) [44.00 to 519.00]	139.50 (48.00 to 364.00) [1.00 to 1856.00]	64.00 (44.00 to 504.00) [36.00 to 519.00]
Missing data	2	0	0	0	2	0
Maximal grade, No. (%)						
No.	59	3	65	3	124	6
Mild	53 (89.8)	3 (100)	58 (89.2)	3 (100)	111 (89.5)	6 (100)
Moderate	6 (10.2)	0	7 (10.8)	0	13 (10.5)	0
Severe	0	0	0	0	0	0
Localization of inflammation, No. (%)						
No.	59	3	65	3	124	6
Anterior chamber inflammation	35 (59.3)	3 (100)	40 (61.5)	2 (66.7)	75 (60.5)	5 (83.3)
Intermediate inflammation	24 (40.7)	0	25 (38.5)	1 (33.3)	49 (39.5)	1 (16.7)
Posterior inflammation	0	0	0	0	0	0
Eyes with at least 1 elevation of IOP, No. (%)	14 (45.2)	5 (16.1)	7 (22.6)	0 (0.0)	21 (33.9)	5 (8.1)
No. of elevations of IOP events	16	5	8	0	24	5
Duration, d						
No.	14	3	8	0	22	3
Mean (SD)	228.8 (277.4)	96.3 (70.3)	215.9 (274.4)	0	224.1 (269.8)	96.3 (70.3)
Median (IQR) [range]	172.50 (29.00 to 281.00) [1.00 to 968.00]	64.00 (48.00 to 177.00) [48.00 to 177.00]	55.00 (2.00 to 473.50) [1.00 to 665.00]	0	130.50 (12.00 to 457.00) [1.00 to 968.00]	64.00 (48.00 to 177.00) [48.00 to 177.00]
Missing data	2	2	0	0	2	2
Maximal grade, No. (%)						
No.	16	5	8	0	24	5
Mild	12 (75.0)	4 (80.0)	6 (75.0)	0	18 (75.0)	4 (80.0)
Moderate	4 (25.0)	1 (20.0)	2 (25.0)	0	6 (25.0)	1 (20.0)
Severe	0	0	0	0	0	0

Abbreviations: AESI, adverse event of special interest; IOP, intraocular pressure; RESCUE, Efficacy Study of Lenadogene Nolparvovec for the Treatment of Vision Loss Up to 6 Months From Onset in LHON Due to the *MT-ND4* Mutation; REVERSE, Efficacy Study of Lenadogene Nolparvovec for the Treatment of Vision Loss From 7 Months to 1 Year From Onset in LHON Due to the *MT-ND4* Mutation.

and Bin Li group, Wuhan, China) reported the same contralateral effect seen with lenadogene nolparvovec,[20-22] indicating that this is a reproducible phenomenon and not an isolated occurrence.

Overall, eyes treated with lenadogene nolparvovec and eyes treated with sham gained +22 ETDRS letters and +20 ETDRS letters vs nadir at 5 years after treatment, indicating that the treated and untreated eyes tracked together. Patient responder rates were globally approximately 70%, including the clinically relevant recovery, endorsed by an International Committee of LHON experts,[13] and based on the published literature.[23-25]

Interestingly, when comparing the evolution of BVCA over time between the 152 eyes of participants in the RESCUE, REVERSE, and RESTORE trials and the 408 eyes of natural history patients with LHON due to the *MT-ND4* gene variant, the analysis at the last available observation showed a statistically significant and clinically meaningful better BCVA in the treated pool vs the natural history pool, with no overlap of the 95% CI. The conservative threshold of at least 15 ETDRS letters (−0.3 logMAR) difference, endorsed by regulators, has been used to define the clinically meaningfulness of the difference.[26] Patients from the natural history pool were matched for age (≥15 years at onset of vision loss) and LHON

genotype (symptomatic LHON due to the m.11778G>A variant) with patients from the RESCUE, REVERSE, and RESTORE trials for a meaningful comparison.[10,11]

The longer-lasting efficacy of lenadogene nolparvovec was reflected by a sustained improvement in participants' QoL, as demonstrated by a meaningful improvement from baseline in 7 of 10 NEI VFQ-25 subscale scores, and a mean gain of 7 points in the composite score at 5 years.

In this follow-up study including 62 patients with LHON due to the *MT-ND4* gene variant, no systemic treatment- or procedure-related AEs were reported, and ocular AEs were mostly mild with no cases of severe or serious AEs or AEs that led to study discontinuation. The frequency of the 2 AESI, intraocular inflammation and increased IOP, was lower after 2 years of gene therapy administration than before, which is consistent with the global ocular safety profile of lenadogene nolparvovec and confirms the absence of delayed safety issues.[27] The good safety profile of lenadogene nolparvovec over time after administration was also reported in the 5-year open-label dose-escalation study REVEAL,[3] and it is consistent with previously published 7-year follow-up data from Yuan and colleagues[21] on another AAV2-*ND4* gene therapy.

Limitations

This study has some limitations. A major limitation of the results is that the change in BCVA after intervention used change in BCVA from the previous lowest level of BCVA (the previous nadir) rather than from the baseline BCVA. The problem with using the nadir is that the nadir will be the worse BCVA across multiple BCVA tests, and it could be 1 low BCVA 1 time due to poor effort or fixation, especially when measuring BCVA at these relatively poor levels of vision, such as a Snellen equivalent of 20/800. In turn, one explanation for improvement from the nadir could be regression to the mean, that is, the BCVA improved from 1 BCVA obtained at 1 time, which was low due to poor effort or fixation. Another major limitation of this study includes the lack of a control group of untreated patients raising difficulties in interpreting the actual treatment effect. However, the comparison of unilaterally treated patients with LHON due to the *MT-ND4* gene variant vs an external control group of untreated patients with natural history of LHON matched for age and *MT-ND4* genotype showed the efficacy of lenadogene nolparvovec in improving BCVA compared with the spontaneous natural decline observed in untreated patients. Other limitations should also be mentioned. First, the patients were unmasked after database lock of the RESCUE and REVERSE trials, as the communication of treatment assigned to each eye was permitted. This unmasking could have introduced bias. Nevertheless, the evolution of outcome measures between year 2 and year 5 showed a similar improvement for eyes treated with lenadogene nolparvovec as for eyes treated with sham, suggesting that this unmasking had no impact on the study results. Second, because of the long follow-up duration of the study, potential bias due to loss of follow-up cannot be ruled out. In addition, choosing the nadir as the reference value could have led to an underestimate of the improvement in BCVA from nadir in cases where the nadir could have been missed (before the baseline or between visits), and conversely, to a better improvement in BCVA from nadir when compared from baseline if the nadir value was worse than the baseline value. There was no multiplicity adjustment and in the case of a missing BCVA value at a specific time point, a manual review of visits with an available BCVA value was carried out to decide which visit to use before database lock and data analyses. The imbalance between female and male participants, which is a classical feature of the population of individuals with LHON, made the comparison between genders difficult. Finally, the use of a last observed carried forward method for missing BCVA values is also a limitation as more sophisticated methods for handling missing data are now available.

In summary, the absence of a control arm secondary to the contralateral therapeutic effect of lenadogene nolparvovec and the variability of baseline BCVA related to treatment administration during the early acute phases of the disease brought challenges in the assessment of the efficacy of lenadogene nolparvovec. Therefore, an indirect comparison approach was used to compare patients treated with lenadogene nolparvovec with an external control group, comparable in terms of age and gene variant. The favorable evolution of BCVA over time and the amplitude of improvement vs nadir in patients with LHON due to the *MT-ND4* gene variant treated with the gene therapy have never been achieved in comparable untreated patients with the *MT-ND4* gene variant. Importantly, the follow-up of patients with LHON due to the *MT-ND4* gene variant who were unilaterally treated with lenadogene nolparvovec demonstrated the persistence of lenadogene nolparvovec effect when compared with an external control group, and a favorable safety profile, up to 5 years after treatment.

Conclusions

LHON due to the *MT-ND4* gene variant is the most frequent and severe clinical form of LHON with a high unmet medical need. The evidence of persistent benefit over time with lenadogene nolparvovec is promising for the use of gene therapy in patients with LHON due to the *MT-ND4* gene variant.

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Invited Commentary

Single-Eye Gene Therapy for Leber Hereditary Optic Neuropathy

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Leber hereditary optic neuropathy (LHON) is typified by an abrupt, painless beginning of vision loss that mostly affects central vision. Severe vision impairment usually develops quickly, and many individuals have substantial bilateral central scotomas. While a small percentage of patients spontaneously recover somewhat, most continue to have vision impairments. After the initial phase, visual acuity usually stabilizes, leaving a significant number of patients with persistent vision impairment to varied degrees. The variability of the natural history has been a challenge for the clinical development of therapies.

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LHON is caused by mutations in the mitochondrial genome, most commonly the *ND4* gene. Various forms of gene augmentation therapies are being developed, which aim to express a healthy copy of the mitochondrial ND4 protein. Notably, 3 phase 3 clinical trials already have been completed. In this issue of *JAMA Ophthalmology*, Yu-Wai-Man et al[1] present the 5-year outcomes from a phase 3 clinical trial using lenadogene nolparvovec gene therapy in m.11778G>A MT-ND4-LHON. The RESTORE trial involved participants from the RESCUE[2] and REVERSE[3] phase 3 clinical trials. The key finding from this study is that the sustained bilateral improvement observed at the 2-year mark after unilateral injection appeared to persist up to 5 years posttreatment.

The initial findings of the RESCUE and REVERSE trials showed somewhat puzzling results because none of the primary outcomes for the 2 trials were met, despite improvement in various parameters. This discrepancy was associated with a prespecified primary outcome, specifically, the best-corrected visual acuity (BCVA) difference between treated and control (fellow) eyes. Both trials resulted in improved BCVA, but improvement was noted in both the study eye and the fellow (control) eyes.

The potentially durable effect of lenadogene nolparvovec might come as no surprise, as the adenoassociated viral (AAV) vectors are designed to induce long-term, stable gene expression in nondividing cells, such as retinal ganglion cells or photoreceptors. This phenomenon was evident in voretigene neparvovec, an AAV-based gene therapy for *RPE65* mutation-associated inherited retinal dystrophy, reporting functional vision improvement up to 7.5 years, the latest tested time point.[4]