Predictors of Final Visual Outcome in Patients With Leber Hereditary Optic Neuropathy Treated With Lenadogene Nolparvovec Gene Therapy

Robert C. Sergott,[1] Valerio Carelli,[2,3] Nancy J. Newman,[4] Valérie Biousse,[4] Patrick Yu-Wai-Man,[5–8] Catherine Vignal-Clermont,[9,10] Constant Josse,[11] Magali Taiel,[12] José-Alain Sahel,[9,13–16] and Piero Barboni[17,18]; for the LHON Study Group

[1]Departments of Ophthalmology and Neurology, Wills Eye Hospital; William H. Annesley, Jr., EyeBrain Center, Thomas Jefferson University, Philadelphia, Pennsylvania, United States
[2]IRCCS Istituto delle Scienze Neurologiche di Bologna, Programma di Neurogenetica, Bologna, Italy
[3]Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy
[4]Departments of Ophthalmology, Neurology and Neurological Surgery, Emory University School of Medicine, Atlanta, Georgia, United States
[5]Cambridge Centre for Brain Repair and MRC Mitochondrial Biology Unit, Department of Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom
[6]Cambridge Eye Unit, Addenbrooke's Hospital, Cambridge University Hospitals, Cambridge, United Kingdom
[7]Moorfields Eye Hospital, London, United Kingdom
[8]UCL Institute of Ophthalmology, University College London, London, United Kingdom
[9]Department of Neuro Ophthalmology and Emergencies, Rothschild Foundation Hospital, Paris, France
[10]Centre Hospitalier National D'Ophtalmologie des Quinze-Vingts, Paris, France
[11]eXYSTAT, Malakoff, France
[12]GenSight Biologics, Paris, France
[13]Sorbonne Université, INSERM, CNRS, Institut de la Vision, Paris, France
[14]Fondation Ophtalmologique A. de Rothschild, Paris, France
[15]Department of Ophthalmology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States
[16]Centre Hospitalier National D'Ophtalmologie des Quinze-Vingts, Institut Hospitalo-Universitaire FOReSIGHT, INSERM-DGOS CIC, Paris, France
[17]IRCCS San Raffaele Scientific Institute, Milan, Italy
[18]Studio Oculistico d'Azeglio, Bologna, Italy

Correspondence: Robert C. Sergott, Departments of Ophthalmology and Neurology, Wills Eye Hospital, 840 Walnut Street, Suite 930, Philadelphia, PA 19107, USA; rcs220@comcast.net.

See the Appendix for the members of the LHON Study Group.

Received: March 31, 2025
Accepted: June 18, 2025
Published: July 15, 2025

Citation: Sergott RC, Carelli V, Newman NJ, et al. Predictors of final visual outcome in patients with Leber hereditary optic neuropathy treated with lenadogene nolparvovec gene therapy. *Invest Ophthalmol Vis Sci.* 2025;66(9):42. https://doi.org/10.1167/iovs.66.9.42

Purpose. This exploratory analysis aimed to identify predictive factors of final best-corrected visual acuity (BCVA) in patients with Leber hereditary optic neuropathy (LHON) harboring the m.11778G>A mutation who received lenadogene nolparvovec gene therapy.

Methods. The following covariates were individually evaluated as possible factors associated with improved final BCVA: age, gender, timing of treatment, baseline BCVA value, and baseline optical coherence tomography (OCT) parameters. Univariate analyses were performed from three phase 3 studies (RESCUE, REVERSE, and REFLECT), using BCVA at 1.5 years post-treatment as the dependent variable.

Results. In 113 eyes treated at least 6 months after disease onset, the covariates statistically significantly associated with an improvement in final BCVA after having reached a nadir were thicker OCT measurements at baseline—specifically, outer segments of the macular ganglion cell layer (GCL) (superior, temporal, inferior, and nasal) and retinal nerve fiber layer (RNFL) quadrants (superior, inferior, and nasal) ($P < 0.05$). The largest effects were observed in the thickness of the superior outer GCL segments at baseline (−0.28 logMAR; 95% confidence interval [CI], −0.41 to −0.16) and temporal outer GCL segments at baseline (−0.26 logMAR; 95% CI, −0.38 to −0.13; both $P < 0.001$). A better baseline BCVA in the dynamic phase of the disease was associated with a better final BCVA (−0.09 logMAR; 95% CI, −0.11 to −0.08; $P < 0.0001$).

Conclusions. Better baseline BCVA values and baseline thicker GCL and RNFL at OCT measurements are key predictive factors of the improved BCVA 1.5 years after treatment in patients with MT-*ND4* LHON who received lenadogene nolparvovec at least 6 months after disease onset.

iovs.arvojournals.org | ISSN: 1552-5783

Investigative Ophthalmology & Visual Science

Keywords: LHON, gene therapy, lenadogene nolparvovec, predictors, optical coherence tomography

Leber hereditary optic neuropathy (LHON), the most common mitochondrial disease, is estimated to affect 1 in 30,000 people.[1] Patients generally present with rapidly progressive visual loss due to selective retinal ganglion cell (RGC) degeneration leading to optic nerve atrophy.[2,3] The disease is characterized by a specific pattern of retinal nerve fiber layer (RNFL) thickening and early ganglion cell layer (GCL) thinning during the subacute stage (6 months from onset), followed by progressive RNFL thinning in the dynamic stage (6–12 months) which stabilizes in the chronic stage (>12 months).[4–6] Cellular degeneration is caused by mitochondrial dysfunction due, in about 90% of cases, to three mtDNA point mutations that affect complex I subunits: m.11778G>A in MT-*ND4*, m.3460G>A in MT-*ND1*, and m.14484T>C in MT-*ND6*.[1,7]

The natural history of LHON may include some occurrences of spontaneous recovery of visual function from the lowest value of best-corrected visual acuity (BCVA) reached during the subacute phase (nadir) of the disease, most often in patients carrying the m.14484T>C pathogenic variant and in cases with childhood onset.[8,9] Recent metanalyses of LHON patients carrying the most frequent m.11778G>A pathogenic variant estimated spontaneous recovery in 11% of patients ages 15 years or older.[10]

LHON is characterized by male prevalence and incomplete penetrance, suggesting that modifying factors contribute to disease onset,[3] including genetic modifying factors, hormonal modulation of mitochondrial function,[11,12] and environmental triggers such as tobacco smoking.[13,14] Thus, LHON seems to be sensitive to multiple modifying factors that may regulate disease onset as well as the propensity to different prognostic outcomes.

Therapeutic options are currently limited to administration of the quinone analog idebenone, which bypasses complex I dysfunction and limits excessive reactive oxygen species production.[15,16] Idebenone therapy is approved in Europe, United Kingdom, Switzerland, and Israel but not by the U.S. Food and Drug Administration.

Lenadogene nolparvovec is an investigational gene therapy for LHON patients carrying the m.11778G>A MT-*ND4* mutation, the most common and severe causative mutation. This gene therapy aims to restore the activity of dysfunctional complex I by reintroducing wild-type MT-*ND4* within mitochondria.[10,17] Intravitreal injection of a recombinant adeno-associated virus (AAV) serotype 2 vector carrying a replacement MT-*ND4* recoded transgene enables nuclear allotopic expression of the wild-type MT-*ND4* gene and its import into RGC mitochondria. The efficacy and safety of lenadogene nolparvovec were evaluated in three phase 3 studies, which showed that a single unilateral injection resulted in a reproducible recovery in BCVA from nadir in the treated eye, but also unexpectedly in the untreated eye.[18–24] These studies also showed better visual outcome in patients treated between 6 and 12 months after disease onset (REVERSE study),[19] as compared to patients treated earlier, within 6 months after onset (RESCUE study).[18] This other unexpected observation was also confirmed by the trial comparing bilateral to unilateral treatment (REFLECT study).[20]

Analyzing the data from MT-*ND4* LHON patients who received lenadogene nolparvovec in the REVERSE, RESCUE, and REFLECT trials, the present study utilized spectral-domain optical coherence tomography (SD-OCT) and other clinical outcomes to identify predictive factors of BCVA changes 1.5 years after treatment.

Methods

Patients and Data Collection

The methodologies of the three phase 3 RESCUE, REVERSE, and REFLECT studies have been described in previous publications.[18–20,23] REVERSE and RESCUE were two phase 3 pivotal trials designed to evaluate the efficacy of a single intravitreal injection of lenadogene nolparvovec in recently affected patients (up to 12 months of vision loss) with a follow-up of 96 weeks after treatment administration. The right eye of each subject was randomly allocated to receive either gene therapy or sham treatment in a 1:1 allocation ratio. The fellow (left) eye received the treatment not allocated to the right eye. The main difference between the two studies was the onset of vision loss: from 181 to 365 days (6–12 months) in REVERSE and up to 180 days (0–6 months) in RESCUE.[18,19] A phase 3 pivotal study, REFLECT, was conducted to assess the efficacy of a bilateral intravitreal injection of lenadogene nolparvovec. All patients had vision loss for up to 1 year at the time of treatment administration. Patients received an intravitreal injection (IVT) of lenadogene nolparvovec in the first affected eye and were randomly allocated to an IVT of either gene therapy or placebo in the second affected eye.[20,23]

BCVA was assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 1 or 4 meters. Off-chart values were converted into logarithm of the minimum angle of resolution (logMAR) using the Lange correspondence (counting fingers, logMAR +2.0; hand motion, logMAR +2.3),[25] and logMAR +4.0 and +4.5 for light perception and no light perception, respectively. SD-OCT scans of the macula and the optic nerve were performed for each eye after pupil dilation with the SPECTRALIS OCT (Heidelberg Engineering, Heidelberg, Germany) as per standard protocols included in the SPECTRALIS software. Retinal GCL thickness within the inner and outer macular regions (not including RNFL and inner plexiform layer) and peripapillary and papillomacular bundle (PMB) RNFL thicknesses in affected LHON patients were the studied predefined OCT outcomes. The OCT metrics were measured and graded by a masked central ophthalmology reading center (Central Reading Center, Annesley EyeBrain Center, Vickie and Jack Farber Neuroscience Institute for Neuroscience at Thomas Jefferson University, Philadelphia, PA, USA). The OCT assessments were performed using triplicate scans of high quality ($Q > 20$). Borders of the retinal layers were manually adjusted when automated segmentation errors were detected. The protocol for segmentation was as follows. For GCL, segmentation included nine segments as defined by the ETDRS grid[26]: four outer segments of the macula

Investigative Ophthalmology & Visual Science

(superior, temporal, inferior, and nasal), four inner segments of the macula (superior, temporal, inferior, and nasal), and fovea. For RNFL, segmentation included five segments: peripapillary (superior, temporal, inferior, and nasal) and PMB. The grading of the OCTs was performed without knowledge of the patients' visual acuity, visual fields, or treatment status.

Statistical Analyses

The predefined baseline for BCVA and OCT parameters was the last available assessment before treatment. Comparisons of OCT parameter evolution were assessed with the absolute change from baseline to 1.5 years post-treatment. *P* values were obtained using a linear model adjusted for the value of the baseline parameter. To consider the intra-patient correlation that exists between both eyes, repeated measures on patients were performed when both eyes were included in the analysis.

The predefined univariate analyses consisted of assessing specific covariates with BCVA logMAR continuous value at 1.5 years post-treatment as the dependent variable. The following baseline covariates were evaluated: age, gender, patient's time from vision loss (first affected eye) to treatment (by 1 month), baseline BCVA logMAR value (by 0.1 logMAR), baseline GCL fovea (by 1 µm), baseline outer and inner GCL segments (superior, temporal, inferior, and nasal) (by 5 µm) and RNFL quadrants (superior, temporal, inferior, and nasal), and PMB (by 5 µm). Associations between baseline characteristics and BCVA at 1.5 years were explored using a repeated-measures analysis of variance (ANOVA) on patients, with a "variance components" covariance structure. Analyses were performed for all eyes: lenadogene nolparvovec–treated eyes ("treated eyes"), sham/placebo-treated eyes ("untreated eyes"), and for subgroups according to the timing of gene therapy administration for the first affected eye (within or at least 6 months of vision loss). Missing data at 1.5 years were not imputed and are included in each table.

Results

Participants Characteristics

Overall, the pooled population from the RESCUE, REVERSE, and REFLECT studies included 174 m.11778G>A MT-*ND4* patients who were predominantly male (79.9%) and in their 30s, with a mean ± SD age of 33.5 ± 14.5 years (range, 15–74 years) (Table 1). According to each study design, the mean time from disease onset to treatment was 4.5 ± 1.4 months for RESCUE (patients included within 6 months of vision loss), 10.4 ± 1.7 months for REVERSE (patients included within 6 to 12 months of vision loss), and 8.3 ± 3.2 months for REFLECT, where the time from onset to treatment had to be less than 1 year.

At baseline, the mean BCVA was 1.49 ± 0.48 logMAR for all eyes, 1.53 ± 0.47 logMAR in lenadogene nolparvovec–treated eyes, and 1.43 ± 0.48 logMAR in sham/placebo-

Table 1. Patient Baseline Characteristics Per Study and Overall (Treated and Untreated Eyes)

	RESCUE (*N* = 39)	REVERSE (*N* = 37)	REFLECT (*N* = 98)	Total (*N* = 174)
Gender, *n* (%)				
Female	7 (17.95)	8 (21.62)	20 (20.41)	35 (20.11)
Male	32 (82.05)	29 (78.38)	78 (79.59)	139 (79.89)
Age (y)				
Mean ± SD	36.33 ± 15.49	34.19 ± 15.24	32.11 ± 13.80	33.50 ± 14.52
Median	35.00	30.00	28.50	29.00
Q1–Q3	22.00–47.00	21.00–45.00	21.00–41.00	21.00–45.00
Range	15.00–69.00	15.00–67.00	15.00–74.00	15.00–74.00
Time from disease onset (first affected eye) (months) to injection				
Mean ± SD	4.49 ± 1.36	10.41 ± 1.70	8.33 ± 3.21	7.91 ± 3.29
Median	4.14	10.91	8.89	8.26
Q1–Q3	3.55–5.98	9.13–11.86	5.52–11.63	4.93–11.14
Range	2.30–6.54	6.93–12.85	1.71–11.96	1.71–12.85
BCVA value (logMAR) at baseline				
Mean ± SD	1.27 ± 0.52	1.56 ± 0.36	1.55 ± 0.47	1.49 ± 0.48
Median	1.30	1.55	1.50	1.50
Q1–Q3	1.00–1.60	1.40–2.00	1.20–2.00	1.20–2.00
Range	−0.20 to 2.00	0.70–2.30	0.00–2.30	−0.20 to 2.30
GCL macular volume (mm^3) at baseline				
Mean ± SD	0.72 ± 0.17	0.52 ± 0.07	0.60 ± 0.13	0.61 ± 0.15
Median	0.68	0.52	0.59	0.59
Q1–Q3	0.59–0.83	0.47–0.57	0.50–0.70	0.50–0.70
Range	0.47–1.27	0.36–0.72	0.35–1.00	0.35–1.27
RNFL average thickness (µm) at baseline				
Mean ± SD	98.28 ± 18.45	68.72 ± 17.94	80.76 ± 28.98	82.13 ± 26.71
Median	100.00	68.50	77.00	82.00
Q1–Q3	86.00–109.00	55.00–82.00	56.50–98.50	59.00–101.00
Range	47.00–159.00	39.00–115.00	37.00–200.00	37.00–200.00

Descriptive statistics of BCVA, GCL macular volume, and RNFL average thickness were performed at eye level. Results are for 348 eyes from 174 patients, with no missing data.

Investigative Ophthalmology & Visual Science

Table 2. Outcomes at 1.5 Years After Lenadogene Nolparvovec Administration Split by Treatment Status (Treated and Untreated Eyes)

	Lenadogene Nolparvovec ($N = 222$)	Sham/Placebo ($N = 126$)	P^*	Total ($N = 348$)
BCVA value (logMAR)			0.153	
N	181	109		290
Mean ± SD	1.39 ± 0.55	1.43 ± 0.56		1.41 ± 0.55
Median	1.40	1.40		1.40
Q1–Q3	1.00–1.60	1.20–1.60		1.10–1.60
Range	−0.10 to 2.30	−0.20 to 4.00		−0.20 to 4.00
Missing data	41	17		58
BCVA change from nadir (logMAR)			0.160	
N	181	109		290
Mean ± SD	−0.37 ± 0.39	−0.30 ± 0.30		−0.35 ± 0.36
Median	−0.30	−0.30		−0.30
Q1–Q3	−0.50 to −0.10	−0.40 to −0.10		−0.50 to −0.10
Range	−2.40 to 0.00	−1.10 to 0.00		−2.40 to 0.00
Missing data	41	17		58
GCL macular volume (mm^3)			0.001	
N	169	102		271
Mean ± SD	0.54 ± 0.09	0.51 ± 0.09		0.53 ± 0.09
Median	0.52	0.50		0.51
Q1–Q3	0.48–0.58	0.44–0.55		0.47–0.57
Range	0.34–0.87	0.31–0.84		0.31–0.87
Missing data	53	24		77
GCL macular volume (mm^3) change from baseline			0.001	
N	169	102		271
Mean ± SD	−0.07 ± 0.14	−0.12 ± 0.15		−0.09 ± 0.14
Median	−0.07	−0.09		−0.08
Q1–Q3	−0.15 to 0.01	−0.19 to −0.02		−0.16 to 0.00
Range	−0.50 to 0.34	−0.61 to 0.12		−0.61 to 0.34
Missing data	53	24		77
RNFL average thickness (µm)			0.123	
N	174	105		279
Mean ± SD	50.51 ± 13.80	48.82 ± 15.19		49.87 ± 14.33
Median	47.00	44.00		46.00
Q1–Q3	41.00–56.00	39.00–51.00		41.00–54.00
Range	31.00–100.00	32.00–113.00		31.00–113.00
Missing data	48	21		69
RNFL average thickness (µm) change from baseline			0.123	
N	174	105		279
Mean ± SD	−30.03 ± 25.39	−35.07 ± 22.66		−31.93 ± 24.48
Median	−24.00	−33.00		−27.00
Q1–Q3	−47.00 to −9.00	−51.00 to −16.00		−49.00 to −12.00
Range	−103.00 to 9.00	−94.00 to 1.00		−103.00 to 9.00
Missing data	48	21		69

The nadir was defined as the worst BCVA value from baseline to the time of the final assessment. No data imputation was performed.
* *P* value for the difference between lenadogene nolparvovec–treated eyes and sham/placebo-treated eyes. *P* values were obtained using a linear model adjusted for baseline parameter values.

treated eyes (Supplementary Table S1). On average, baseline BCVA was better in RESCUE (1.27 ± 0.52 logMAR) than in REVERSE (1.56 ± 0.36 logMAR) or REFLECT (1.55 ± 0.47 logMAR) (Table 1).

GCL macular volume and RNFL average thickness at baseline were similar between treated and untreated eyes, with mean GCL macular volumes of 0.61 ± 0.14 and 0.62 ± 0.16 mm^3 and RNFL average thicknesses of 80.83 ± 26.79 and 84.41 ± 26.51 µm, respectively (see Supplementary Table S1). The GCL macular volume and RNFL thickness were higher in RESCUE (0.72 ± 0.17 mm^3 and 98.28 ± 18.45 µm, respectively) than in REVERSE (0.52 ± 0.07 mm^3 and 68.72 ± 17.94 µm, respectively) or REFLECT (0.60 ± 0.13 mm^3 and 80.76 ± 28.98 µm, respectively) (Table 1).

Outcomes at 1.5 Years After Gene Therapy Administration According to the Treatment Status

At 1.5 years after treatment, eyes that received gene therapy reached a mean BCVA value of 1.39 ± 0.55 logMAR, whereas eyes that received sham/placebo reached a mean BCVA of 1.43 ± 0.56 logMAR ($P = 0.153$) (Table 2). A mean improvement in BCVA from nadir (worst BCVA from baseline to 1.5 years) of −0.37 ± 0.39 logMAR (+19 ETDRS letters) was observed in treated eyes and −0.30 ± 0.30 logMAR (+15 ETDRS letters) in sham/placebo eyes ($P = 0.160$).

Overall, mean GCL macular volume decreased by −0.09 ± 0.14 mm^3 from baseline, with a statistically significant reduced thinning in lenadogene nolparvovec–treated eyes

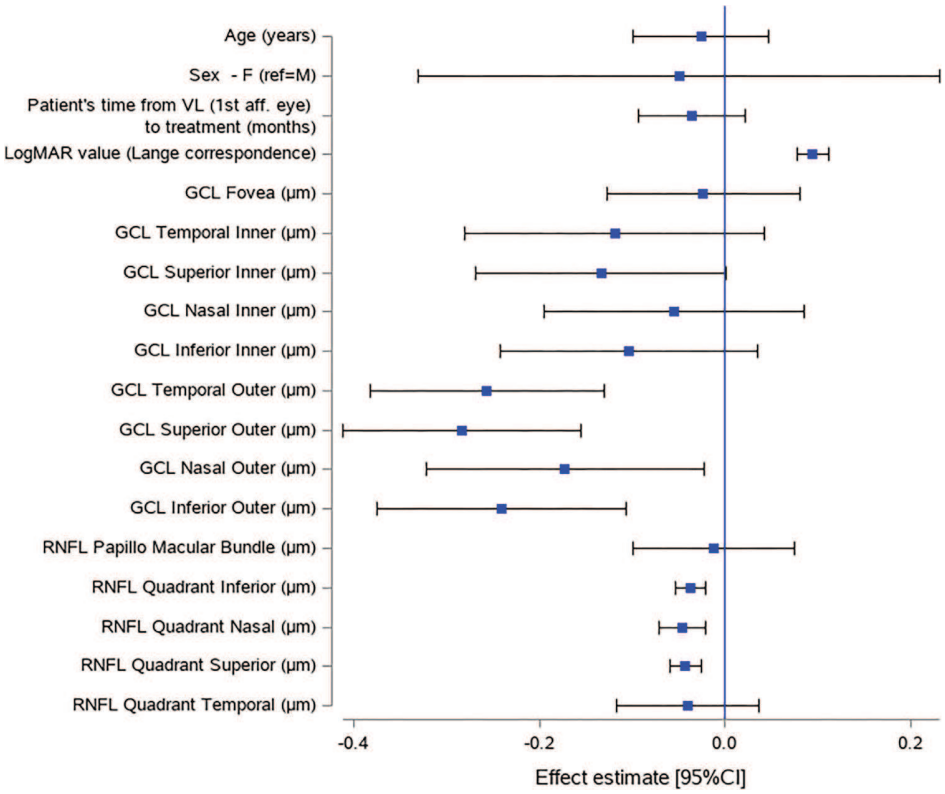

Figure 1. Forest plots of univariate analyses with BCVA at 1.5 years as dependent variable and baseline characteristics (age, gender, timing of treatment, BCVA value, and OCT parameters) as independent variables in eyes treated with lenadogene nolparvovec at least 6 months after disease onset. The analyses were performed in eyes showing the optimal benefit of lenadogene nolparvovec (i.e., in eyes treated with gene therapy after 6 months from vision loss; 113 eyes). All of the independent variables were continuous except gender (male/female); the dependent variable was continuous. For the continuous independent variables (age, time from vision loss, BCVA value, and OCT parameters at baseline), the forest plot illustrates the difference in BCVA for a variation of a predefined number of units, whereas for the categorical variable (gender) it represents the difference in BCVA between the two categories (male/female). The predefined number of units for independent variables were 10 years for age, 1 month for time from vision loss, 0.1 logMAR for BCVA value, 1 µm for GCL fovea, and 5 µm for all other OCT parameters. Missing data were not imputed. The logMAR values and OCT parameters were assessed at baseline. F, female; M, male; VL, vision loss.

versus sham/placebo-treated eyes (−0.07 ± 0.14 vs. −0.12 ± 0.15 mm^3; $P = 0.001$). Additionally, RNFL average thickness decreased by −31.93 ± 24.48 µm from baseline, with a reduced thinning in ledanogene nolparvovec–treated eyes versus sham/placebo-treated eyes (−30.03 ± 25.39 vs. −35.07 ± 22.66 µm; $P = 0.123$) (Table 2).

Outcomes at 1.5 Years After Gene Therapy Administration According to the Timing of Treatment

At 1.5 years post-treatment, the mean BCVA value was statistically better in eyes treated at least 6 months after vision loss than in eyes treated within 6 months of vision loss (1.37 ± 0.53 vs. 1.47 ± 0.58 logMAR; $P < 0.001$). Eyes treated at least 6 months after vision loss showed a mean improvement from nadir of −0.36 ± 0.36 logMAR (+18 letters), with an improvement of −0.38 ± 0.38 logMAR (+19 letters) in lenadogene nolparvovec–treated eyes and −0.32 ± 0.32 logMAR (+16 letters) in sham/placebo-treated eyes ($P = 0.333$); eyes treated within 6 months after vision loss showed a mean improvement from nadir of −0.32 ± 0.37 logMAR (+16 letters), with an improvement of −0.35 ± 0.43 logMAR (+18 letters) in lenadogene nolparvovec–treated eyes and −0.28 ± 0.28 logMAR (+14 letters) in sham/placebo-treated eyes ($P = 0.323$) (Supplementary Table S2).

Eyes treated at least 6 months after onset showed a statistically significant smaller reduction from baseline compared with eyes treated within 6 months after onset in GCL volume (−0.01 ± 0.09 vs. −0.20 ± 0.14 mm^3; $P < 0.001$) and in RNFL average thickness (−17.39 ± 13.88 vs. −52.36 ± 21.37 µm; $P < 0.001$). Furthermore, in eyes treated at least 6 months after onset, the thinning of mean GCL macular volume and RNFL average thickness was statistically significantly more limited in lenadogene nolparvovec–treated eyes as compared to sham/placebo-treated eyes (mean GCL macular volume change from baseline: −0.00 ± 0.09 mm^3 and −0.03 ± 0.08 mm^3, respectively; $P = 0.006$; RNFL average thickness: −15.40 ± 13.16 µm and −21.29 ± 14.53 µm, respectively; $P = 0.013$) (Supplementary Table S2).

Predictive Factors of BCVA at 1.5 Years

Univariate analyses were conducted to identify factors predictive of BCVA 1.5 years after treatment in the subgroup of eyes showing the best response to gene therapy (best improvement in BCVA from nadir at 1.5 years)—that is, eyes treated with lenadogene nolparvovec at least 6 months after disease onset.

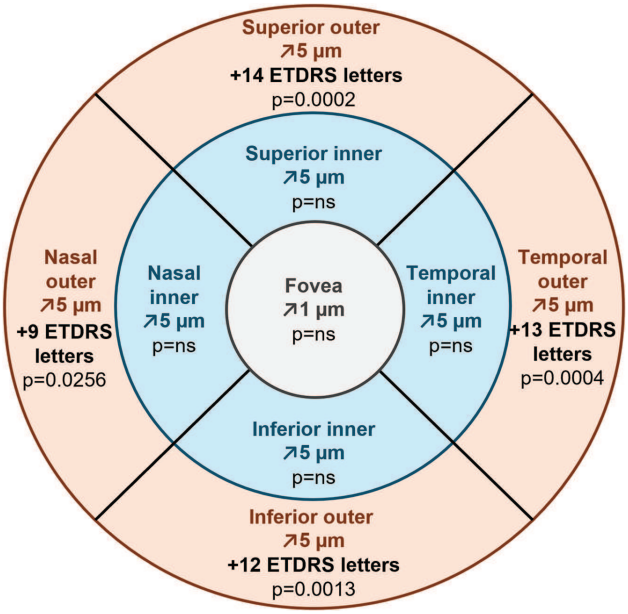

Figure 2. Results of univariate analyses with BCVA at 1.5 years as the dependent variable and baseline characteristics as the independent variables in eyes treated with lenadogene nolparvovec at least 6 months after disease onset on the nine macular GCL segments at baseline; ns, not significant. According to the ETDRS grid, the retina was divided into nine segments defined by three rings: a central foveal ring, an inner macular ring, and an outer macular ring. The inner and outer rings were divided into four quadrants: superior, temporal, inferior, and nasal.[26] The association of the thickness of each macular GCL segment at baseline with BCVA 1.5 years after gene therapy administration was studied using univariate analyses in eyes treated at least 6 months after disease onset. Each 5-µm increase in the thickness of the four outer segments (superior, temporal, inferior, and nasal) of the macular GCL at baseline was statistically significantly associated with an improvement in final BCVA of +9 to +14 ETDRS letters, depending on the segment.

Greater thickness of all four outer segments of the macular GCL (superior, temporal, inferior, and nasal) and three RNFL quadrants (superior, inferior, and nasal) at baseline were statistically significantly associated with better final BCVA ($P < 0.05$) (Fig. 1). The strongest effects were observed with respect to the thickness of the superior and temporal segments of the outer macular ring, with each 5-µm thickening at baseline associated with an estimated 0.28 logMAR (95% confidence interval [CI], −0.41 to −0.16; +14 letters) and 0.26 logMAR (95% CI, −0.38 to −0.13; +13 letters) improvement of the final BCVA at 1.5 years post-treatment ($P < 0.001$), respectively (Fig. 2, Table 3). A better baseline BCVA in the dynamic phase of the disease was associated with a better final BCVA, with an effect estimate of −0.09 logMAR (95% CI, −0.11 to −0.08; +5 letters) for each 0.1 logMAR (+5 letters) of baseline BCVA ($P < 0.0001$). Other patient characteristics, including age, gender, and timing of treatment administration within the 6- to 12-month window, were not predictive of final BCVA (Table 3).

Discussion

The aim of this exploratory study was to identify predictive factors of final BCVA in patients with MT-*ND4* LHON who received lenadogene nolparvovec gene therapy in clinical studies. First, we investigated the functional (BCVA) and structural (OCT) outcomes at 1.5 years post-treatment in the eyes that received gene therapy versus those that were treated with sham/placebo. At 1.5 years post-treatment, eyes treated with lenadogene nolparvovec showed a mean improvement in BCVA from nadir of +18 ETDRS letters, which was not statistically different from eyes treated with sham/placebo (gain of 15 ETDRS letters). The contralateral therapeutic effect of lenadogene nolparvovec on untreated eyes has been described in all clinical trials.[18–24] Bilateral improvement after unilateral treatment was also observed with other similar AAV-based therapy products developed by two independent research groups (Guy et al. group, Bascom Palmer Eye Institute, Miami, FL, USA; Li et al. group, Wuhan, China),[27–30] acknowledging a consistent and reproducible effect of AAV-based intravitreal gene therapy in MT-*ND4* LHON. This is further supported by non-human primate data that demonstrated viral vector DNA in both eyes, suggesting transfer from one eye to the other, and the recent demonstration of transfection of the contralateral untreated eye in postmortem analyses of the eyes and visual pathways in two MT-*ND4* LHON patients treated unilaterally with gene therapy (Carelli V, ARVO oral presentation, 2025, 510).[19,31] In our exploratory analysis of OCT parameters, we demonstrated a statistically significant lower reduction in GCL macular volume and a numerically lower decrease in RNFL average thickness of eyes that received lenadogene nolparvovec compared to sham/placebo eyes. These findings suggest that direct injection of gene therapy might better preserve structurally the RGCs and the retinal layers than indirect exposure of the contralateral eye. At the functional level, the results of BCVA in clinical trials also indicate that the efficacy of a direct treatment seems superior to that of its contralateral effect, with numerically better final BCVA values observed in treated eyes compared with untreated eyes.[18–24] Thus, structural and functional evidence concurs that direct injection of lenadogene nolparvovec may be more effective than the contralateral therapeutic effect.

Second, we analyzed BCVA and OCT parameters 1.5 years after treatment according to the timing of gene therapy administration (within vs. after 6 months of vision loss). We found that patients who received lenadogene nolparvovec after 6 months from disease onset reached a statistically better logMAR value than patients who were treated within 6 months since disease onset. This corroborates the 1.5-year results of the RESCUE, REVERSE, and REFLECT studies, which showed better visual outcomes in patients treated during the dynamic phase of the disease (6–12 months since onset; REVERSE patients and most REFLECT patients) compared to patients treated during the subacute phase (0–6 months since onset; RESCUE patients).[18–20] Carelli et al.[22] performed a multivariate analysis of lenadogene nolparvovec–treated patients and reported similar results with a better response for a delayed treatment; the effect estimate on the final BCVA was approximately 1 letter (−0.0217 logMAR; 95% CI, −0.0400 to −0.0035; $P = 0.0200$) for each month of delayed treatment within the therapeutic window of 1 year after disease onset. These results contradict the assumption that administering gene therapy as early as possible after disease onset would maximize its efficacy, as more RGCs presumably would be preserved and repairable. One possible explanation could be that, during the subacute phase of the disease, RNFL pseudoedema may hamper the diffusion of the viral vector to RGCs.[18] After 6 months, the retinal layers stabilize, with the end of thinning of the inner plexiform layer and GCL,[5,32] which may

Investigative Ophthalmology & Visual Science

Table 3. Univariate Analyses With BCVA at 1.5 Years As Dependent Variable and Baseline Characteristics (Age, Gender, Timing of Treatment, BCVA Value, and OCT Parameters) as Independent Variables (Eyes Treated With Lenadogene Nolparvovec After At Least 6 months Since Disease Onset)

Covariate	*N*	Effect Estimate (95% CI)	Least Square Mean (95% CI)	*P*
Age (by 10 y)	113	−0.026 (−0.1, 0.047)		0.4744
Gender				0.7245
Female (reference = male)	19	−0.05 (−0.332, 0.231)	1.31 (1.05, 1.57)	
Male	94		1.36 (1.25, 1.48)	
Patient's time from vision loss (first affected eye) to treatment (by 1 month)	113	−0.036 (−0.093, 0.021)		0.2137
Baseline logMAR value (by 0.1 logMAR)	113	0.094 (0.077, 0.111)		**<0.0001**
GCL parameters at baseline				
GCL fovea (by 1 µm)	113	−0.024 (−0.127, 0.08)		0.6374
GCL temporal inner (by 5 µm)	113	−0.119 (−0.281, 0.042)		0.1397
GCL superior inner (by 5 µm)	113	−0.134 (−0.269, 0.001)		0.0518
GCL nasal inner (by 5 µm)	113	−0.056 (−0.196, 0.085)		0.4180
GCL inferior inner (by 5 µm)	113	−0.104 (−0.243, 0.035)		0.1341
GCL temporal outer (by 5 µm)	112	−0.257 (−0.383, −0.13)		**0.0004**
GCL superior outer (by 5 µm)	113	−0.284 (−0.413, −0.156)		**0.0002**
GCL nasal outer (by 5 µm)	113	−0.173 (−0.323, −0.023)		**0.0256**
GCL inferior outer (by 5 µm)	113	−0.241 (−0.376, −0.107)		**0.0013**
RNFL parameters at baseline				
RNFL papillo macular bundle (by 5 µm)	113	−0.012 (−0.099, 0.075)		0.7752
RNFL quadrant inferior (by 5 µm)	113	−0.037 (−0.054, −0.021)		**0.0001**
RNFL quadrant nasal (by 5 µm)	113	−0.046 (−0.071, −0.022)		**0.0008**
RNFL quadrant superior (by 5 µm)	113	−0.043 (−0.06, −0.026)		**<0.0001**
RNFL quadrant temporal (by 5 µm)	113	−0.04 (−0.117, 0.036)		0.2827

No data imputation was performed.

contribute to greater efficiency in transfection of remaining dormant RGCs able to respond to gene therapy. Other patient characteristics were not predictive of response treatment.[22] Although idebenone therapy has a different mechanism of action than lenadogene nolparvovec, recent data suggest that its administration in later (dynamic/chronic) stages as compared to the subacute stage might also result in better visual outcomes in m.11778G>A MT-*ND4* LHON patients (Romagnoli M, et al., oral presentation at EUROMIT 2023 meeting). If the better effectiveness of idebenone therapy parallels that of lenadogene nolparvovec in relation to timing of therapy administration from disease onset, further understanding of what truly hampers the response to any therapy in the first several months after onset of LHON is needed. The hypothesis that axonal pseudoedema represents a physical barrier for the diffusion of the viral vector would not explain the results from idebenone administration, given that this is an orally administered drug, thereby implicating a more systemic or cell autonomous underlying mechanism.

Our analysis of OCT parameters according to the timing of gene therapy administration showed less thinning of the GCL and RNFL from baseline to 1.5 years for patients treated during the dynamic phase compared to patients treated during the subacute phase. This limited thinning of OCT layers during the dynamic phase could be related to the effect of lenadogene nolparvovec, the known natural history of OCT parameter evolution previous to treatment, or both. It is important to note that the GCL macular volume and average RNFL thickness at 1.5 years post-treatment were similar in eyes that received gene therapy, whatever the timing of lenadogene nolparvovec administration. In the dynamic phase of the disease, the retinal layers as imaged on OCT appear to be sufficiently preserved to enable the effects of therapy, as this translates functionally into better visual outcomes in patients treated after 6 months since vision loss compared with patients treated within 6 months since vision loss.

From two-subgroup analyses, we determined that the eyes of LHON patients that seem most likely to benefit from lenadogene nolparvovec were those directly injected with the gene therapy at least 6 months after disease onset. In this subgroup of patients, we found that certain SD-OCT parameters at baseline were predictive of BCVA 1.5 years after gene therapy administration. Each 5-µm preservation in the thickness of the four outer segments (superior, temporal, inferior, and nasal) of the macular GCL and three RNFL quadrants (superior, inferior, and nasal) at baseline was statistically significantly associated with an improvement in final BCVA of +2 to +14 letters (depending on the segment/quadrant; $P < 0.05$ for outer segments of the macular GCL, and $P \leq 0.001$ for RNFL quadrants). A stronger predictive effect was observed with macular GCL thickness, specifically of the superior and temporal outer segments, than with RNFL thickness, corroborating several studies showing that GCL structural integrity is a better predictor of visual function in LHON patients compared with other OCT measures.[32–36] To date, our understanding of the relationship between changes in OCT parameters and visual function outcomes in treated and untreated LHON patients remains incomplete. Different RNFL, GCL, or inner plexiform layer parameters have reportedly been associated with visual outcomes.[33,34,37,38] Our results support the existence of a relationship between better GCL and RNFL preservation at baseline and final visual outcome in MT-*ND4* patients treated with gene therapy at least 6 months after disease onset, unequivocally linking structure with function.

Baseline BCVA was also statistically significantly associated with final BCVA in eyes treated with lenadogene nolparvovec during the dynamic stage of the disease, a better

baseline value predicting a better value at 1.5 years post-treatment. Similarly, Borrelli et al.[34] also identified baseline BCVA as an important predictor of long-term BCVA in LHON patients treated with idebenone. One could postulate that a better baseline BCVA could correspond to a selection of patients with less severe disease evolution, MT-*ND4* LHON disease being by itself heterogeneous in terms of outcome; indeed, the individual spontaneous evolution of the disease could be a confounding factor of the assessment of baseline BCVA as a predictive factor of outcome.

The main limitations of our study include its exploratory nature and the absence of a pure sham/placebo control group that could have provided insights on predictive factors of outcome of the spontaneous evolution of MT-*ND4* LHON disease. Additionally, patients were treated within 1 year after vision loss in lenadogene nolparvovec trials, limiting our findings to a timing of administration of gene therapy during the subacute and dynamic phases of the disease.

In conclusion, this exploratory study, by linking structure and function, improves our understanding of the factors influencing vision recovery after lenadogene nolparvovec administration in patients with MT-*ND4* LHON, showing that better baseline BCVA values and thicker baseline OCT retinal layers in the dynamic phase of the disease, particularly the outer segments of macular GCL, are the key predictive factors associated with better BCVA 1.5 years after treatment in patients who received gene therapy at least 6 months after disease onset. This relationship between preservation of retinal structures and response to treatment strongly supports an effect of lenadogene nolparvovec on RGC survival and function. These findings should facilitate optimization of patient selection for future clinical trials.

Acknowledgments

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

Supported by an Advanced Fellowship Award from the UK National Institute of Health Research (NIHR) (NIHR301696 to PY-W-M); Fight for Sight (PY-W-M); Isaac Newton Trust (PY-W-M); Moorfields Eye Charity (GR001376 to PY-W-M); Addenbrooke's Charitable Trust (PY-W-M); National Eye Research Centre (PY-W-M); International Foundation for Optic Nerve Disease (PY-W-M); NIHR as part of the Rare Diseases Translational Research Collaboration (PY-W-M); NIHR Cambridge Biomedical Research Centre (NIHR203312 to PY-W-M); NIHR Biomedical Research Centre based at Moorfields Eye Hospital National Health Service (NHS) Foundation Trust and UCL Institute of Ophthalmology (NIHR203322 to PY-W-M); a grant from LifeArc, a charity registered in England and Wales (10748); and by GenSight Biologics. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

Author Contributions: R.C.S., V.C., C.J., M.T., J.A.S. and P.B. contributed to the conception and design of the study; R.C.S., V.C., N.J.N., V.B., P.Y.-W.-M., C.V.-C., C.J., M.T., J.-A.S. and P.B. contributed to the acquisition and analysis of data; R.C.S., V.C., N.J.N., C.J., M.T., J.-A.S. and P.B. contributed to drafting the manuscript.

Disclosure: **R.C. Sergott**, GenSight Biologics (C); **V. Carelli**, GenSight Biologics (C), Chiesi (C), Pretzel Therapeutics (C); **N.J. Newman**, GenSight Biologics (C, F), Chiesi (C), Neurophth (C); **V. Biousse**, GenSight Biologics (C); **P. Yu-Wai-Man**, GenSight Biologics (C), Chiesi (C), Neurophth (C); **C. Vignal-Clermont**, GenSight Biologics (C), Chiesi (C); **C. Josse**, None; **M. Taiel**, GenSight Biologics (E); **J.-A. Sahel**, GenSight Biologics (I, O, R), allotopic expression (P); **P. Barboni**, None

References

1. Yu-Wai-Man P, Votruba M, Burté F, La Morgia C, Barboni P, Carelli V. A neurodegenerative perspective on mitochondrial optic neuropathies. *Acta Neuropathol*. 2016;132(6):789–806.
2. Carelli V, Carbonelli M, de Coo IF, et al. International consensus statement on the clinical and therapeutic management of Leber hereditary optic neuropathy. *J Neuroophthalmol*. 2017;37(4):371–381.
3. Borrelli E, Bandello F, Boon CJF, et al. Mitochondrial retinopathies and optic neuropathies: the impact of retinal imaging on modern understanding of pathogenesis, diagnosis, and management. *Prog Retin Eye Res*. 2024;101:101264.
4. Barboni P, Carbonelli M, Savini G, et al. Natural history of Leber's hereditary optic neuropathy: longitudinal analysis of the retinal nerve fiber layer by optical coherence tomography. *Ophthalmology*. 2010;117(3):623–627.
5. Balducci N, Savini G, Cascavilla ML, et al. Macular nerve fibre and ganglion cell layer changes in acute Leber's hereditary optic neuropathy. *Br J Ophthalmol*. 2016;100(9):1232–1237.
6. Carbonelli M, La Morgia C, Romagnoli M, et al. Capturing the pattern of transition from carrier to affected in Leber hereditary optic neuropathy. *Am J Ophthalmol*. 2022;241:71–79.
7. Carelli V, Ghelli A, Zanna C, Baracca A, Sgarbi G, Martinuzzi A. Severe defect of complex I-dependent ATP synthesis shapes the mitochondria-driven path of apoptotic cell death in Leber's hereditary optic neuropathy (LHON). *Invest Ophthalmol Vis Sci*. 2004;45(13):1624.
8. Mackey D, Howell N. A variant of Leber hereditary optic neuropathy characterized by recovery of vision and by an unusual mitochondrial genetic etiology. *Am J Hum Genet*. 1992;51(6):1218–1228.
9. Barboni P, La Morgia C, Cascavilla ML, et al. Childhood-onset Leber hereditary optic neuropathy—clinical and prognostic insights. *Am J Ophthalmol*. 2023;249:99–107.
10. Newman NJ, Carelli V, Taiel M, Yu-Wai-Man P. Visual outcomes in Leber hereditary optic neuropathy patients with the m.11778G>A (*MTND4*) mitochondrial DNA mutation. *J Neuroophthalmol*. 2020;40(4):547–557.
11. Giordano C, Iommarini L, Giordano L, et al. Efficient mitochondrial biogenesis drives incomplete penetrance in Leber's hereditary optic neuropathy. *Brain*. 2014;137(pt 2):335–353.
12. Giordano C, Montopoli M, Perli E, et al. Oestrogens ameliorate mitochondrial dysfunction in Leber's hereditary optic neuropathy. *Brain*. 2011;134(pt 1):220–234.
13. Carelli V, d'Adamo P, Valentino ML, et al. Parsing the differences in affected with LHON: genetic versus environmental triggers of disease conversion. *Brain*. 2016;139(pt 3):e17.
14. Kirkman MA, Yu-Wai-Man P, Korsten A, et al. Gene–environment interactions in Leber hereditary optic neuropathy. *Brain*. 2009;132(pt 9):2317–2326.
15. Klopstock T, Yu-Wai-Man P, Dimitriadis K, et al. A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy. *Brain*. 2011;134(pt 9):2677–2686.
16. Carelli V, La Morgia C, Valentino ML, et al. Idebenone treatment in Leber's hereditary optic neuropathy. *Brain*. 2011;134(pt 9):e188.
17. Vignal C, Uretsky S, Fitoussi S, et al. Safety of rAAV2/2-ND4 gene therapy for Leber hereditary optic neuropathy. *Ophthalmology*. 2018;125(6):945–947.
18. Newman NJ, Yu-Wai-Man P, Carelli V, et al. Efficacy and safety of intravitreal gene therapy for Leber hereditary

optic neuropathy treated within 6 months of disease onset. *Ophthalmology*. 2021;128(5):649–660.
19. Yu-Wai-Man P, Newman NJ, Carelli V, et al. Bilateral visual improvement with unilateral gene therapy injection for Leber hereditary optic neuropathy. *Sci Transl Med*. 2020;12(573):eaaz7423.
20. Newman NJ, Yu-Wai-Man P, Subramanian PS, et al. Randomized trial of bilateral gene therapy injection for m.11778G>A MT-ND4 Leber optic neuropathy. *Brain*. 2023;146(4):1328–1341.
21. Biousse V, Newman NJ, Yu-Wai-Man P, et al. Long-term follow-up after unilateral intravitreal gene therapy for Leber hereditary optic neuropathy: the RESTORE study. *J Neuroophthalmol*. 2021;41(3):309–315.
22. Carelli V, Newman NJ, Yu-Wai-Man P, et al. Indirect comparison of lenadogene nolparvovec gene therapy versus natural history in patients with Leber hereditary optic neuropathy carrying the m.11778G>A *MT-ND4* mutation. *Ophthalmol Ther*. 2023;12(1):401–429.
23. Subramanian PS, Newman NJ, Moster M, et al. Study design and baseline characteristics for the reflect gene therapy trial ofm.11778g>A/*ND4*-LHON. *BMJ Open Ophthalmol*. 2022;7(1):e001158.
24. Newman NJ, Yu-Wai-Man P, Carelli V, et al. Intravitreal gene therapy vs. natural history in patients with Leber hereditary optic neuropathy carrying the m.11778G>A *ND4* mutation: systematic review and indirect comparison. *Front Neurol*. 2021;12:662838.
25. Lange C, Feltgen N, Junker B, Schulze-Bonsel K, Bach M. Resolving the clinical acuity categories "hand motion" and "counting fingers" using the Freiburg Visual Acuity Test (FrACT). *Graefes Arch Clin Exp Ophthalmol*. 2009;247(1):137–142.
26. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology*. 1991;98(5 suppl):786–806.
27. Guy J, Feuer WJ, Davis JL, et al. Gene therapy for Leber hereditary optic neuropathy: low- and medium-dose visual results. *Ophthalmology*. 2017;124(11):1621–1634.
28. Lam BL, Feuer WJ, Davis JL, et al. Leber hereditary optic neuropathy gene therapy: adverse events and visual acuity results of all patient groups. *Am J Ophthalmol*. 2022;241:262–271.
29. Yang S, Ma SQ, Wan X, et al. Long-term outcomes of gene therapy for the treatment of Leber's hereditary optic neuropathy. *EBioMedicine*. 2016;10:258–268.
30. Wan X, Pei H, Jian ZM, et al. Efficacy and safety of rAAV2-ND4 treatment for Leber's hereditary optic neuropathy. *Sci Rep*. 2016;6(1):21587.
31. Calkins DJ, Yu-Wai-Man P, Newman NJ, et al. Biodistribution of intravitreal lenadogene nolparvovec gene therapy in nonhuman primates. *Mol Ther Methods Clin Dev*. 2021;23:307–318.
32. Moster SJ, Moster ML, Scannell Bryan M, Sergott RC. Retinal ganglion cell and inner plexiform layer loss correlate with visual acuity loss in LHON: a longitudinal, segmentation OCT analysis. *Invest Ophthalmol Vis Sci*. 2016;57(8):3872–3883.
33. Zeng K, Chou B, Sadun AA. Minimum ganglion cell layer thickness is the best structural predictor of visual function in Leber hereditary optic neuropathy. *Med Res Arch*. 2023;11(7):10.18103/mra.v11i7.1.4107.
34. Borrelli E, Berni A, Cascavilla ML, et al. Visual outcomes and optical coherence tomography biomarkers of vision improvement in patients with Leber hereditary optic neuropathy treated with idebenone. *Am J Ophthalmol*. 2023;247:35–41.
35. Battista M, Coutinho CP, Berni A, et al. Sectorial ganglion cell complex thickness as biomarker of vision outcome in patients with dominant optic atrophy. *Invest Ophthalmol Vis Sci*. 2024;65(1):24.
36. Hedström J, Nilsson M, Engvall M, Williams PA, Venkataraman AP. Ganglion cell complex thickness and visual function in chronic Leber hereditary optic neuropathy. *Invest Ophthalmol Vis Sci*. 2024;65(12):4.
37. Yuan J, Zhang Y, Chen C, et al. Association between visual function and optic fiber layer thickness after gene therapy for Leber hereditary optic neuropathy. *Chinese J Exp Ophthalmol*. 2022;12:908–913.
38. Pemp B, Mitsch C, Kircher K, Reitner A. Changes in visual function and correlations with inner retinal structure in acute and chronic Leber's hereditary optic neuropathy patients after treatment with idebenone. *J Clin Med*. 2021;10(1):151.

Appendix. The LHON Study Group

James Acheson, Jasmina Al-Tamami, Giulia Amore, Shweta Anand, Andre Aun, George Baker Hubbard, Francesco Bandello, Rudrani Banik, Piero Barboni, Megan Barrett, Marco Battista, Valérie Biousse, Hayley Boston, Asma Burale, Francesca Calcagno, Michele Carbonelli, Valerio Carelli, Maria Lucia Cascavilla, Lorena Castillo, Claudia B. Catarino, Dean Cestari, Celia Chen, Hui-Chen Cheng, Steve Cho, Bart K. Chwalisz, Manuela Contin, Pietro D'Agati, Michael Dattilo, Adam A. DeBusk, Julie De Zaeytijd, Lidia Di Vito, Jannah Dobbs, Sean P. Donahue, Lindreth DuBois, Maria Eleftheriadou, Simona Esposti, Alcides Fernandes Filho, Rod Foroozan, Elizabeth Fortin, Sapna Gangaputra, Virginia Garcia, Maria Gemenetzi, Deborah Gibbs, Jean François Girmens, Rabih Hage, Julia A. Haller, Eman Hawy, Gad Heilweil, Andrew M. Hendrick, Martin Hildebrandt, Rima Hussain, Jeong-Min Hwang, Laia Jaumendreu Urquijo, Rasha Jorany, Neringa Jurkute, Rustum Karanjia, Wahiba Khemliche, Thomas Klopstock, Chiara La Morgia, Lauren Leitch-Devlin, Bart P. Leroy, Stéphanie Leruez, Maria Massini, Marc Mathias, Muhammad A Memon, Susan Mohamed, Antonio Morilla, Francisco J. Muñoz Negrete, Daniel Muth, Michael Neuenhahn, Nancy J. Newman, Ghazala O'Keefe, Shriji Patel, Paula Pecen, Jason H. Peragallo, Adelaide Pina, Lise Plaine, Angelika Pressler, Mary Preston, Claudia Priglinger, Siegfried Priglinger, José A. Sahel, Gema Rebolleda Fernández, Martina Romagnoli, Scott Ruark, Günther Rudolph, Alfredo A. Sadun, Melissa SantaMaria, Cosima Schertler, Robert C. Sergott, Priyansha Sheel, Sara Silvestri, Prem S. Subramanian, Chuanbin Sun, Katy Tai, Sarah Thornton, Stephan Thurau, Heather Tollis, Irena Tsui, William R. Tucker, Caroline Van Cauwenbergh, Hilde Verhauwen, Catherine Vignal-Clermont, Bettina von Livonius, An-Guor Wang, Saige Wilkins, Armin Wolf, and Patrick Yu-Wai-Man.

Investigative Ophthalmology & Visual Science