Safety of Lenadogene Nolparvovec Gene Therapy Over 5 Years in 189 Patients With Leber Hereditary Optic Neuropathy

CATHERINE VIGNAL-CLERMONT, PATRICK YU-WAI-MAN, NANCY J. NEWMAN, VALERIO CARELLI, MARK L. MOSTER, VALERIE BIOUSSE, PREM S. SUBRAMANIAN, AN-GUOR WANG, SEAN P. DONAHUE, BART P. LEROY, ALFREDO A. SADUN, THOMAS KLOPSTOCK, ROBERT C. SERGOTT, GEMA REBOLLEDA FERNANDEZ, BART K. CHWALISZ, RUDRANI BANIK, MAGALI TAIEL, MICHEL ROUX, AND JOSÉ-ALAIN SAHEL, ON BEHALF OF THE LHON STUDY GROUP

• PURPOSE: To evaluate the safety profile of lenadogene nolparvovec (Lumevoq) in patients with Leber hereditary optic neuropathy.

• DESIGN: Pooled analysis of safety data from 5 clinical studies.

• METHODS: A total of 189 patients received single unilateral or bilateral intravitreal injections of a recombinant adeno-associated virus 2 (rAAV2/2) vector encoding the human wild-type *ND4* gene. Adverse events (AEs) were collected throughout the studies, up to 5 years. Intraocular inflammation and increased intraocular pressure (IOP) were ocular AEs of special interest. Other assessments included ocular examinations, vector biodissemination, and systemic immune responses against rAAV2/2.

• RESULTS: Almost all patients (95.2%) received 9×10^{10} viral genomes and 87.8% had at least 2 years of follow-up. Most patients (75.1%) experienced at least one systemic AE, but systemic treatment-related AEs occurred in 3 patients; none were serious. Intraocular inflammation was reported in 75.6% of lenadogene nolparvovec-treated eyes. Almost all intraocular inflammations occurred in the anterior chamber (58.8%) or in the vitreous (40.3%), and were of mild (90.3%) or moderate (8.8%) intensity; most resolved with topical corticosteroids alone. All IOP increases were mild to moderate in intensity. No AE led to study discontinuation. Biodissemination of lenadogene nolparvovec and systemic immune response were limited. The safety profile was comparable for patients treated bilaterally and unilaterally.

• CONCLUSIONS: Lenadogene nolparvovec had a good overall safety profile with excellent systemic tolerability,

AJO.com Supplemental Material available at AJO.com.
Accepted for publication November 29, 2022.

From Department of Neuro Ophthalmology and Emergencies, Rothschild Foundation Hospital, Paris, France (C.V-C.); Centre Hospitalier National d'Ophtalmologie des Quinze Vingts, Paris, France (C.V-C.); Cambridge Centre for Brain Repair and MRC Mitochondrial Biology Unit, Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK (P.Y-W-M.); Cambridge Eye Unit, Addenbrooke's Hospital, Cambridge University Hospitals, Cambridge, UK (P.Y-W-M.); UCL Institute of Ophthalmology, University College London, London, UK (P.Y-W-M.); Moorfields Eye Hospital, London, UK (P.Y-W-M.); Departments of Ophthalmology, Neurology and Neurological Surgery, Emory University School of Medicine, Atlanta, GA, USA (N.J.N. and V.B.); IRCCS Istituto delle Scienze Neurologiche di Bologna, Programma di Neurogenetica, Bologna, Italy (V.C.); Unit of Neurology, Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy (V.C.); Departments of Neurology and Ophthalmology, Wills Eye Hospital and Thomas Jefferson University, Philadelphia, PA, USA (M.L.M., R.C.S.); Sue Anschutz-Rodgers University of Colorado Eye Center, University of Colorado School of Medicine, Aurora, CO, USA (P.S.S.); Department of Ophthalmology, Taipei Veterans General Hospital, National Yang Ming Chiao Tung University, Taipei, Taiwan (A-G.W.); Department of Ophthalmology, Neurology, and Pediatrics, Vanderbilt University, and Vanderbilt Eye Institute, Vanderbilt University Medical Center, Nashville, TN, USA (S.P.D.); Department of Ophthalmology and Center for Medical Genetics, Ghent University Hospital, and Department of Head & Skin, Ghent University, Ghent, Belgium (B.P.L.); Doheny Eye Institute, Los Angeles, CA, USA (A.A.S.); Department of Ophthalmology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA (A.A.S.); Friedrich Baur Institute at the Department of Neurology, University Hospital, LMU Munich, Munich, Germany (T.K.); German Center for Neurodegenerative Diseases (DZNE), Munich, Germany (T.K.); Munich Cluster for Systems Neurology (SyNergy), Munich, Germany (T.K.); Department of Ophthalmology, Alcala University, Madrid, Spain (G.R.F.); Department of Ophthalmology, Massachusetts Eye & Ear, Harvard Medical School, Boston, MA, USA (B.K.C.); Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston MA, USA (B.K.C.); Department of Ophthalmology, Icahn School of Medicine at Mount Sinai, New York, NY, USA (R.B.); GenSight Biologics, Paris, France (M.T., M.R.); Sorbonne Université, INSERM, CNRS, Institut de la Vision, Paris, France (J-A.S.); Rothschild Foundation Hospital, Paris, France (J-A.S.); Department of Ophthalmology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA (J-A.S.); Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts, Institut Hospitalo-Universitaire FOReSIGHT, INSERM-DGOS CIC, Paris, France (J-A.S.)

Abbreviations: AAV, adeno-associated virus; AE, adverse event; AESI, adverse event of special interest; BCVA, best-corrected visual acuity; IOP, intraocular pressure; IVT, intravitreal injection; LHON, Leber hereditary optic neuropathy; NAbs, neutralizing antibodies; OIS, ocular inflammation score; Q1, first quartile; Q3, third quartile; rAAV2/2, recombinant adeno-associated virus 2 of serotype 2; SD, standard deviation; vg, viral genome.

Inquiries to Catherine Vignal-Clermont, Foundation Hospital Adolphe de ROTHSCHILD, Department of Neuro Ophthalmology and Emergencies, 29 rue Manin, 75019 Paris, France; e-mail: cvignal@for.paris

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2022.11.026

consistent with limited bio-dissemination. The product was well tolerated, with mostly mild ocular side effects responsive to conventional ophthalmologic treatments. (Am J Ophthalmol 2023;249: 108–125. © 2022 Elsevier Inc. All rights reserved.)

INTRODUCTION

Leber hereditary optic neuropathy (LHON) is a rare, maternally-inherited, genetic mitochondrial disease that leads to subacute bilateral vision loss. Three point mutations in the mitochondrial DNA are responsible for about 90% of LHON cases: m.3460G>A, m.11778G>A, and m.14484T>C in the *MTND1*, *MTND4*, and *MTND6* genes, respectively.[1] These genes code for 3 subunits of the respiratory complex I, and their mutations impair ATP synthesis and increase the production of reactive oxygen species, leading to the degeneration of the vulnerable retinal ganglion cells.[1,2] Clinically, the disease manifests with rapidly progressive painless bilateral loss of central vision, either simultaneously or sequentially in the 2 eyes.[3] The most common LHON mutation is the m.11778G>A-ND4 mutation, which accounts for about 70% of LHON in North America and Europe.[1,4,5]

Since 2015, the only treatment approved in the European Union for LHON is idebenone (Raxone, Santhera GmbH), a synthetic coenzyme Q10 analog that facilitates mitochondrial electron flux in bypassing respiratory complex I.[6,7] Idebenone has been approved under exceptional circumstances, which means that additional studies on long-term effects and safety are necessary.[6] To complement this limited therapeutic arsenal in LHON, alternative therapeutic strategies are being developed, including gene therapy.[8-15] One of these gene therapies is lenadogene nolparvovec (Lumevoq, GenSight Biologics), a recombinant adeno-associated virus 2 of serotype 2 (rAAV2/2) vector encoding the human wild-type *ND4* gene (rAAV2/2-ND4). Lenadogene nolparvovec proposes to permanently correct the m.11778G>A genetic mitochondrial mutation in *MT-ND4* LHON patients, based on the allotopic expression strategy that involves the nuclear expression of the wild-type mitochondrial gene engineered with an additional mitochondrial targeting sequence and results in mRNA translation and co-translocation of the protein into mitochondria.[16,17] With the same objective, 2 other AAV2-ND4 gene therapy vectors are being studied: the rAAV2-ND4 from the Huazhong University of Science and Technology (China)[10-12,18] and the self-complementary scAAV2-P1ND4v2 from the Bascom Palmer Eye Institute of the University of Miami (USA).[13,14]

Five clinical studies were/are being conducted with lenadogene nolparvovec in *MT-ND4* LHON patients: one phase 1/2a dose-finding study evaluating the safety of 4 increasing doses of unilateral intravitreal injection (IVT) of the gene therapy (REVEAL)[19,20]; 2 phase 3 randomized, double-masked, sham-controlled studies assessing the efficacy and safety of a unilateral IVT of the gene therapy (RESCUE and REVERSE)[8,9,21]; 1 ongoing long-term follow-up study of patients treated in the RESCUE and REVERSE studies (RESTORE)[22]; and 1 ongoing phase 3, randomized, double-masked, placebo-controlled study evaluating the efficacy and safety of bilateral IVT of lenadogene nolparvovec (REFLECT).[15] Across the 4 phase 3 clinical studies (RESCUE, REVERSE, RESTORE, and REFLECT), both unilateral and bilateral lenadogene nolparvovec induced bilateral improvement in best corrected visual acuity (BCVA) up to 3 years after treatment administration,[8,9,15,20-22] and until 5 years for the very first patients who received treatment in the phase 1/2 study.[17]

This manuscript presents the pooled safety data from the 5 clinical studies with lenadogene nolparvovec, providing an overview of its safety profile in a large group of 189 patients with LHON over a 5-year period.

METHODS

• **SAFETY POPULATION AND CLINICAL STUDIES:** A total of 189 LHON patients received single unilateral or bilateral IVT of lenadogene nolparvovec in 5 clinical studies (3 completed and 2 ongoing) and were followed for up to 5 years. The clinical studies included REVEAL (NCT02064569, completed), RESCUE (NCT02652767, completed), REVERSE (NCT02652780, completed), RESTORE (NCT03406104, ongoing), and REFLECT (NCT03293524, ongoing) (Figure 1). According to the inclusion criteria of the studies, all patients carried the m.11778G>A-ND4 mutation and were at least 15 years old. No restriction on the duration of vision loss was stipulated in REVEAL, whereas vision loss had to be ≤1 year in RESCUE, REVERSE, and REFLECT. Patients could not have known mutations in genes involved in pathological retinal conditions, glaucoma, and optic neuropathy other than LHON; entire mitochondrial and nuclear genome sequencing was not required. Ocular surgery of clinical relevance within 90 days and treatment by idebenone within 7 days prior to enrollment were exclusion criteria.

All the studies were conducted in accordance with the Good Clinical Practice of the International Council for Harmonisation and with applicable local requirements. Each study protocol was approved by an Institutional Review Board/Ethics Committee and written informed consent was obtained from each patient at screening.

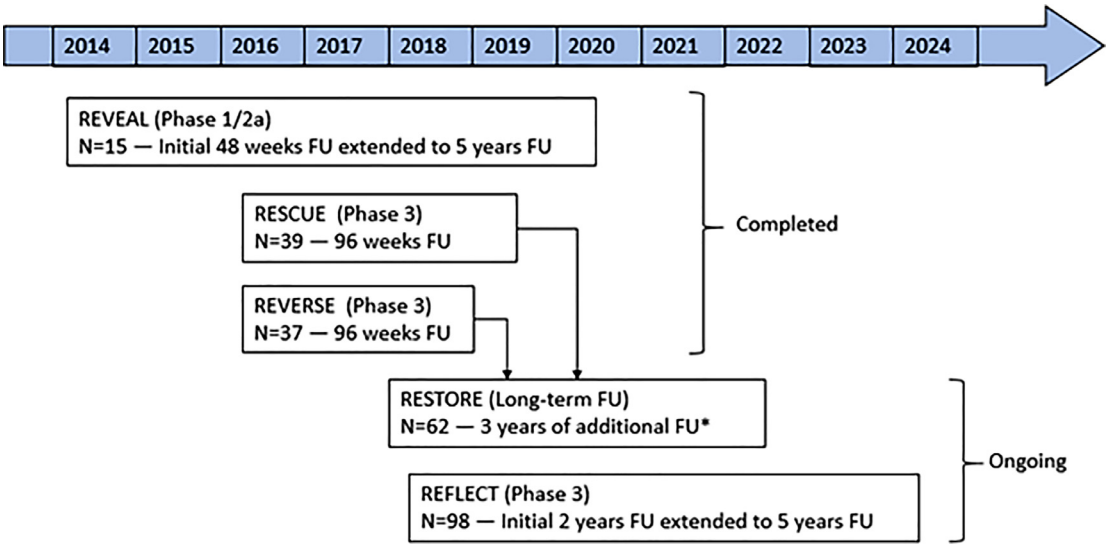

FIGURE 1. Clinical development program of lenadogene nolparvovec. Timelines are based on first patient first visit/last patient last visit (estimated dates for ongoing studies). FU = follow-up; N = number of patients. *RESTORE evaluates the long-term safety of patients treated in RESCUE or REVERSE studies for a total of 5 years post-treatment administration.

• **TREATMENT ADMINISTRATION:** Lenadogene nolparvovec or rAAV2/2-ND4 (Lumevoq, GenSight Biologics) consists of a suspension of purified viral vector formulated in balanced sterile saline solution plus Pluronic F68. In the phase 1/2 open-label REVEAL study, patients were unilaterally injected with 180 μL of 1 of the studied doses of lenadogene nolparvovec: 9×10^9, 3×10^{10}, 9×10^{10}, and 1.8×10^{11} viral genomes (vg)/eye. In RESCUE and REVERSE, patients received an IVT of 90 μL of lenadogene nolparvovec at a dose of 9×10^{10} vg into 1 eye. In REFLECT, patients received either an IVT of lenadogene nolparvovec (9×10^{10} vg/eye in 90 µL) in both eyes or lenadogene nolparvovec in 1 eye and IVT of 90 µL of placebo (balanced sterile saline solution) in the second eye. In the phase 3 studies (RESCUE, REVERSE, and REFLECT), the allocation of treatment was unmasked at the time of the primary efficacy endpoint analyses (48 weeks for RESCUE and REVERSE, and 1.5 years for REFLECT). To prevent increased intraocular pressure (IOP) due to the volume of the injection, an anterior chamber paracentesis was performed aseptically under local anesthesia immediately before the IVT in REVEAL. In all the phase 3 studies, an IOP lowering agent of the investigator's choice was systematically administered before treatment. Patients in REFLECT received oral corticosteroids for 28 days starting 2 days prior to IVT as a peri-treatment for the prevention or reduction of ocular inflammation related to IVT. This preventive corticosteroid treatment was not used in REVEAL, RESCUE, and REVERSE studies. Pre-IVT procedures in all studies included pupil dilation, use of peri-ocular antisepsis, and topical anesthesia.

• **SAFETY ASSESSMENTS:** Adverse events

Adverse events (AEs) were collected throughout the patient's participation in the studies (ie, up to 5 years after treatment) and described by the investigator regarding the nature, severity (mild, moderate, severe), seriousness, and causal relationship to the study treatment or the study procedure (unrelated, unlikely, possible, or probable). The assessment of relationship to the study procedure referred to any procedure performed in the study and was not restricted to the IVT. Neurological AEs were considered as systemic adverse events of special interest (AESIs). Ocular AESIs included intraocular inflammation and increased IOP.

Ocular assessments

Ocular examinations were performed at baseline, immediately after injection, and at 2, 4, 8, 12, and 24 weeks and 1, 1.5, 2, 2.5, 3, 4, and 5 years after administration of lenadogene nolparvovec. The IOP of each eye was measured using applanation tonometry. Slit lamp biomicroscopy examinations were performed before and after pupil dilation. Anatomic location, severity, and clinical evolution of intraocular inflammation were assessed according to the Standardization of Uveitis Nomenclature[23] for anterior chamber cells and flare and vitreous cells, and to the National Institutes of Health Grading Scale for vitreous haze.[24] At baseline and at each post-treatment visit, eyes were graded for determination of 4 separate inflammation subscores (anterior chamber cell score, anterior chamber flare score, vitreous cell score, and vitreous haze score) using a scale from 0 (no inflammation) to 4 (highest inflammation). A composite global ocular inflammation score (OIS) was then cal-

culated for each eye by adding the 4 separate subscores, leading to a global score ranging from 0 (no inflammation) to 16 (highest inflammation). Anterior chamber cells and flare, and vitreous cells were graded during slit lamp examinations. Vitreous haze was graded based on color fundus photos of the posterior pole of each eye.

Vital signs, physical examinations, and laboratory tests

Vital signs included blood pressure, pulse rate, and oral temperature. The physical examination consisted of checking the general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, extremities, and body weight of patients. Blood samples were collected at baseline and after administration of the treatment at 1 or 3 days, 2, 4, 8, 12, and 24 weeks and 1, 1.5, 2, 2.5, 3, 4 and 5 years. Laboratory tests included hematology (red blood cells, hemoglobin, hematocrit, white blood cells with differential, and platelets), serum chemistry (glucose, lipase, amylase, calcium, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, and creatinine), and liver function tests (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, and albumin).

Bio-dissemination

In the RESCUE, REVERSE, and REFLECT studies, biodissemination of lenadogene nolparvovec was analyzed in the blood using a specific validated quantitative polymerase chain reaction method targeting the *ND4* transgene. In REVEAL, bio-dissemination was assessed in blood, tears, and urine; the quantified sequence was specific to the cytomegalovirus promoter of the vector.

Immunogenicity

Anti-AAV2 neutralizing antibodies (NAbs) were measured in the serum by a customized seroneutralization assay. Cellular immune response against the rAAV2/2 vector was estimated by interferon gamma enzyme-linked immunospot assay.

• **STATISTICAL METHODS:** All data analyses were performed using SAS version 9.4 (SAS Institute Inc). Descriptive statistics were used: number of filled data, mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), and minimum and maximum for quantitative variables; and number of filled data, frequency, and percentage (referring to filled data) for qualitative variables. Analyses are presented in all exposed patients and by doses at the patient level (189 patients in total) and/or at the eye level (378 eyes in total). No integrated safety analyses were performed for the evaluation of vital signs, physical examinations, bio-dissemination, and immunogenicity. With RESTORE and REFLECT currently ongoing, interim data are presented for both studies (data cut-off date July 12, 2021 for RESTORE [3-year data available in most patients] and all data available at the time of the primary analysis at 1.5 years for REFLECT [ie, >1.5 years as applicable]).

RESULTS

• **SAFETY POPULATION:** The safety population included 189 *MT-ND4* LHON patients who received a single unilateral or bilateral IVT of lenadogene nolparvovec. Of these 189 patients, 49 patients were administered bilaterally in the REFLECT study. Treatment exposure by dose is shown in Table 1. Almost all patients (180 in total) were treated with the dose of 9×10^{10} vg and 166 had at least 2 years of follow-up after gene therapy (87.8%). Thirteen patients (6.9%) were followed-up for 5 years, including 7 patients treated at 9×10^{10} vg. Considering the low number of patients treated with doses other than 9×10^{10} vg (3 patients/dose, ie, 9 patients in REVEAL), the safety data from the 9×10^{10} vg dose and all doses together (9×10^{9}, 3×10^{10}, 1.8×10^{11}, and 9×10^{10} vg/eye) are presented in this manuscript.

• **DEMOGRAPHICS AND DISEASE CHARACTERISTICS:** Demographic data of the safety population are presented in Table 2. Approximately 80% of patients were male and aged between 18 and 60 years. Overall, the mean (SD) age at screening was 35.2 (15.2) years. A total of 18 children (9.5%) were enrolled and aged between 15 and 18 years at screening; all received the 9×10^{10} vg dose. Elderly patients (≥60 years) accounted for less than 8% of the safety population and included 15 patients, 13 of whom were treated at 9×10^{10} vg. The oldest patient was 83.9 years and received a dose of 9×10^{9} vg in the REVEAL study.

The mean (SD) age at onset of LHON was 36.1 (15.2) years for REVEAL, RESCUE, and REVERSE patients treated at 9×10^{10} vg, whereas it was 31.9 years for REFLECT patients. At baseline before injection with lenadogene nolparvovec, nearly all patients (97.4% overall) were affected bilaterally, and the duration of vision loss ranged from 1.7 to 272.5 months (median [Q1-Q3]: 8.7 [5.3-11.6] months). Ten patients from REVEAL had a duration of vision loss longer than 1 year (maximum 23 years), in accordance with the lack of restriction for the duration of vision loss in this study. Mean (SD) BCVA at baseline (expressed in LogMAR) was 1.4 (0.6) for the better eye and 1.7 (0.6) for the worse eye.

• **SYSTEMIC ADVERSE EVENTS:** Many patients (75.1%) experienced at least 1 systemic AE, for a total of 532 events. Most systemic AEs were of mild (69.3%) or moderate (22.2%) intensity and were considered unrelated to the study treatment or procedure. Headache was the most frequent systemic AE, reported by 31 patients (16.4%), closely followed by nasopharyngitis (26 patients, 13.8%).

TABLE 1. Treatment Exposure by Dose – Safety Population.

	Dose 9 x 10^9 vg	Dose 3 × 10^{10} vg	Dose 1.8 × 10^{11} vg	Dose 9 × 10^{10} vg	One Eye At Dose 9 × 10^{10} vg	Both Eyes at Dose 9 × 10^{10} vg	Total
	REVEAL			REVEAL RESCUE REVERSE	REFLECT		REVEAL RESCUE REVERSE REFLECT
	n = 3	*n* = 3	*n* = 3	*n* = 82	*n* = 49	*n* = 49	*n* = 189
Included patients in the safety population	3	3	3	82	49	49	189
Included patients in the pediatric safety population	0	0	0	8	6	4	18
Study recruitment							
REVEAL	3	3	3	6	0	0	15
RESCUE[a]	0	0	0	39	0	0	39
REVERSE	0	0	0	37	0	0	37
REFLECT	0	0	0	0	49	49	98
RESTORE[b]	0	0	0	62	0	0	62
Patients who completed year 1	3 (100)	3 (100)	3 (100)	82 (100)	47 (95.9)	48 (98.0)	186 (98.4)
Patients who completed year 2	2 (66.7)	3 (100)	3 (100)	79 (96.3)	39 (79.6)	40 (81.6)	166 (87.8)
Patients who completed year 3	2 (66.7)	3 (100)	3 (100)	59 (72.0)	3 (6.1)	2 (4.1)	72 (38.1)
Patients who completed year 4	2 (66.7)	3 (100)	3 (100)	35 (42.7)	0 (0.0)	0 (0.0)	43 (22.8)
Patients who completed year 5	(0.0)	3 (100)	3 (100)	7 (8.5)	0 (0.0)	0 (0.0)	13 (6.9)

Data are shown as *n* or *n* (%)

[a]Of the 39 enrolled patients in RESCUE, 1 patient received approximately half dose of the scheduled 9 × 10^{10} vg.

[b]RESTORE is the extension study of RESCUE and REVERSE; no treatment was administered in this study.

TABLE 2. Demographic Characteristics – Safety Population

	Dose 9 × 10^{10} vg	Dose 9 × 10^{10} vg One Eye	Dose 9 × 10^{10} vg Both Eyes	All Doses (1.8 × 10^{11}; 3 × 10^{10}; 9 × 10^{10}; 9 × 10^9)
	REVEAL RESCUE REVERSE (*n* = 82)	REFLECT (*n* = 49)	REFLECT (*n* = 49)	REVEAL RESCUE REVERSE REFLECT (*n* = 189)
Age at screening, years[a]				
Mean (SD)	36.9 (15.6)	32.6 (13.4)	32.5 (14.4)	35.2 (15.2)
Median	35.2	30.3	27.7	30.4
Q1-Q3	22.5-48.0	20.4-41.4	23.2-41.1	22.6-46.9
Range	15.5-71.6	15.0-65.3	15.0-74.6	15.0-83.9
Categories of age at screening, years[a] ***n* (%)**				
<15	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
15-18	8 (9.8)	6 (12.2)	4 (8.2)	18 (9.5)
18-60	66 (80.5)	41 (83.7)	42 (85.7)	156 (82.5)
≥60	8 (9.8)	2 (4.1)	3 (6.1)	15 (7.9)
Gender, *n* (%)				
Female	16 (19.5)	9 (18.4)	11 (22.4)	37 (19.6)
Male	66 (80.5)	40 (81.6)	38 (77.6)	152 (80.4)

[a]Screening visit occurred from 2 days to 4 weeks before treatment.

Other common systemic AEs were increase in gamma-glutamyltransferase (6.3%) or in alanine aminotransferase (3.2%), hypertension (5.8%), and anxiety (4.8%). Seven systemic AEs occurring in 3 patients (1.6%) (1 nausea, 1 nasopharyngitis, 2 toothaches, and 3 headaches) and 24 systemic AEs in 18 patients (9.5%) were assessed as related to the study treatment or study procedure, respectively; none was serious. Eighteen patients experienced at least 1 serious systemic AE, none were thought to be related to the study treatment or procedure. Four deaths (2.1%) were reported in the safety population, all were thought to be unrelated to the study treatment or procedure. No systemic AE led to study discontinuation.

As neurological defects may occur in LHON patients[25-27], neurological AEs were considered systemic AESIs. A total of 47 patients (24.9%) reported at least 1 systemic neurological AE, mostly headache (31 of 47, 66.0%), and less commonly dizziness, migraine, and paresthesia (in 3 of 47, 1.6% patients each). Six serious neurological AEs, all assessed as unrelated to study treatment or procedure, occurred in 5 patients: a case of LHON plus with a Leigh-like phenotype, 2 cases of multiple sclerosis, and 1 psychotic disorder, neurologic entities that have been reported in association with LHON[25-27], and a glioblastoma multiforme in 1 patient (counted as 2 separate events because of recurrence).[28] These serious neurological disorders occurred between 7 months and 3 years after injection of the gene therapy.

Bilateral injection of lenadogene nolparvovec was not associated with differences in the frequency, nature, or severity of systemic AEs compared with unilateral injection.

• **OCULAR ADVERSE EVENTS:** Ocular AEs were more frequent in eyes treated with lenadogene nolparvovec compared with uninjected eyes and placebo eyes (90.3% vs 63.7% and 57.1% of eyes; 858 vs 137 and 52 events) (Table 3). Higher proportions of ocular AEs were assessed as related to the study treatment in lenadogene nolparvovec eyes compared with uninjected/placebo eyes (78.2% vs 13.6%). This trend was less marked for ocular AEs considered related to the study procedure (55.0% of lenadogene nolparvovec eyes vs 37.9% of uninjected/placebo eyes). Most ocular AEs were of mild intensity: 756/858 events for lenadogene nolparvovec eyes (88.1%) and 169/189 events for uninjected/placebo eyes (89.4%). Severe ocular AEs were infrequent and occurred at a comparable frequency between lenadogene nolparvovec eyes and uninjected/placebo eyes: 5 eyes (2.1%) and 2 eyes (1.4%), respectively (Table 3). One patient experienced a serious ocular AE—a retinal tear in the uninjected eye (1.1%)—thought to unlikely be related to the study treatment or procedure, whereas no serious ocular AE was reported in any lenadogene nolparvovec-treated eye. No ocular AE led to study discontinuation in any patient.

The most common ocular AEs related to study treatment were vitritis (lenadogene nolparvovec: 51.7%, uninjected/placebo: 2.1%), iridocyclitis (lenadogene nolparvovec: 27.7%, uninjected/placebo: 3.6%), keratic precipitates (lenadogene nolparvovec: 23.9%, uninjected/placebo: 0.7%) and iritis (lenadogene nolparvovec: 9.7%, uninjected/placebo: none) (Table 4). Punctate keratitis and conjunctival hemorrhage were the most reported ocular AEs related to the study procedure, occurring at a similar frequency in lenadogene nolparvovec eyes and uninjected/placebo eyes (punctate keratitis: 20.6% for lenadogene nolparvovec eyes and 22.9% for uninjected/placebo eyes; conjunctival hemorrhage: 8.0% for lenadogene nolparvovec eyes and 6.4% for uninjected/placebo eyes) (Table 5). Among the AEs considered related to the study procedure, those consisting of ocular inflammation, such as vitritis and iridocyclitis, were more frequently reported in eyes treated with gene therapy (vitritis: 7.6% for lenadogene nolparvovec eyes vs none for the uninjected/placebo eyes; iridocyclitis: 5.0% vs 0.7%).

The ocular safety profile of lenadogene nolparvovec for pediatric patients (15 to 18 years) and the elderly (≥60 years) was similar to the safety profile observed in the overall population.

Intraocular Inflammation

Events of intraocular inflammation, considered as AESIs, were observed in the majority of lenadogene nolparvovec eyes (180 eyes, 75.6%; 432 events) compared with a relatively small number of uninjected and placebo eyes (8 eyes, 8.8%; 13 events and 5 eyes, 10.2%; 6 events, respectively) (Table 6). Most of the intraocular inflammation events were considered related to the study treatment and unrelated/unlikely related to the study procedure. In lenadogene nolparvovec eyes, most inflammation events were of mild (90.3%) or moderate (8.8%) intensity, and 4 were severe (0.9%) (Table 6). The 4 severe intraocular inflammation events occurred in the treated eyes of 2 patients (anterior chamber inflammation and 2 episodes of vitritis in a REVEAL patient's eye; vitritis in a REVERSE patient's eye) and started 12 and 13 days after the injection of the gene therapy; all resolved and were considered probably related to study treatment. All inflammation events reported in uninjected/placebo eyes were of mild intensity.

With the gene therapy product, almost all intraocular inflammations occurred in the anterior chamber (58.8%) or in the vitreous (ie, intermediate uveitis, 40.3%). There were 3 posterior uveitis (retinal vasculitis) (0.7%), see Table 6.

The mean (SD) and median time of occurrence of intraocular inflammation in lenadogene nolparvovec treated eyes was 3.7 (5.0) months and 1.9 months post-treatment, respectively. Among the 432 events of intraocular inflammation, 28 new events occurred beyond 1 year post-treatment: 24 between 1 and 2 years and 4 between 2 and 3 years (Table 7). Intraocular inflammation had a longer duration in lenadogene nolparvovec eyes (median 92 days) compared with uninjected/placebo eyes (median 64 days),

TABLE 3. Summary of Ocular Adverse Events – Safety Population

	Lenadogene Nolparvovec Eye				Uninjected/Placebo Eye					
	Dose 9×10^{10} vg ($n = 229$)		All Doses ($n = 238$)		Total uninjected ($n = 91$)		REFLECT Placebo - Dose 9×10^{10} vg ($n = 49$)		All Doses ($n = 140$)	
	N	E	N	E	N	E	N	E	N	E
At least 1 ocular AE	206 (90.0)	824	215 (90.3)	858	58 (63.7)	137	28 (57.1)	52	86 (61.4)	189
At least 1 ocular AE related to study treatment	179 (78.2)	482	186 (78.2)	505	10 (11.0)	13	9 (18.4)	15	19 (13.6)	28
At least 1 ocular AE related to study procedure	125 (54.6)	259	131 (55.0)	266	38 (41.8)	54	15 (30.6)	20	53 (37.9)	74
At least 1 mild ocular AE	200 (87.3)	723	209 (87.8)	756	57 (62.6)	119	27 (55.1)	50	84 (60.0)	169
At least 1 moderate ocular AE	50 (21.8)	92	51 (21.4)	93	14 (15.4)	16	2 (4.1)	2	16 (11.4)	18
At least 1 severe ocular AE	5 (2.2)	9	5 (2.1)	9	2 (2.2)	2	-	-	2 (1.4)	2
At least 1 serious ocular AE	-	-	-	-	1 (1.1)	1	-	-	1 (0.7)	1
At least 1 ocular AE leading to study discontinuation	-	-	-	-	-	-	-	-	-	-
At least 1 ocular AE leading to death	-	-	-	-	-	-	-	-	-	-
At least 1 AESI	176 (76.9)	474	185 (77.7)	498	12 (13.2)	21	5 (10.2)	8	17 (12.1)	29
At least 1 increased IOP AESI	52 (22.7)	57	60 (25.2)	66	7 (7.7)	8	1 (2.0)	2	8 (5.7)	10
At least 1 intraocular inflammation AESI	173 (75.5)	417	180 (75.6)	432	8 (8.8)	13	5 (10.2)	6	13 (9.3)	19

Data are presented as *n* (%) for number of eyes (N) and *n* for number of events (E)
AE = adverse event; AESI = adverse event of special interest; IOP = intraocular pressure

TABLE 4. Most Frequent (≥ 5%) Ocular Adverse Events Related to Study Treatment by Preferred Term – Safety Population

	Lenadogene Nolparvovec Eye		Uninjected/Placebo Eye		
	Dose 9×10^{10} vg ($n = 229$)	All Doses ($n = 238$)	Total Uninjected ($n = 91$)	REFLECT Placebo - Dose 9×10^{10} vg ($n = 49$)	All Doses ($n = 140$)
Number of eyes with at least 1 ocular adverse event related to treatment	**179 (78.2)**	**186 (78.2)**	**10 (11.0)**	**9 (18.4)**	**19 (13.6)**
Vitritis	117 (51.1)	123 (51.7)	1 (1.1)	2 (4.1)	3 (2.1)
Iridocyclitis	66 (28.8)	66 (27.7)	3 (3.3)	2 (4.1)	5 (3.6)
Keratic precipitates	57 (24.9)	57 (23.9)	-	1 (2.0)	1 (0.7)
Iritis	23 (10.0)	23 (9.7)	-	-	-
Anterior chamber cell	17 (7.4)	17 (7.1)	-	1 (2.0)	1 (0.7)
Anterior chamber inflammation	13 (5.7)	17 (7.1)	-	-	-
Vitreal cells	14 (6.1)	14 (5.9)	1 (1.1)	-	1 (0.7)
Vitreous floaters	12 (5.2)	12 (5.0)	-	1 (2.0)	1 (0.7)

Data are presented as *n* (%)

TABLE 5. Most Frequent (≥ 5%) Ocular Adverse Events Related to Study Procedure by Preferred Term – Safety Population

	Lenadogene Nolparvovec Eye		Uninjected/Placebo Eye		
	Dose 9×10^{10} vg ($n = 229$)	All Doses ($n = 238$)	Total Uninjected ($n = 91$)	REFLECT Placebo - Dose 9×10^{10} vg ($n = 49$)	All Doses ($n = 140$)
Number of eyes with at least 1 ocular adverse event related to procedure	**125 (54.6)**	**131 (55.0)**	**38 (41.8)**	**15 (30.6)**	**53 (37.9)**
Punctate keratitis	49 (21.4)	49 (20.6)	28 (30.8)	4 (8.2)	32 (22.9)
Conjunctival hemorrhage	19 (8.3)	19 (8.0)	3 (3.3)	6 (12.2)	9 (6.4)
Vitritis	18 (7.9)	18 (7.6)	-	-	-
Conjunctival hyperaemia	14 (6.1)	14 (5.9)	6 (6.6)	1 (2.0)	7 (5.0)
Iridocyclitis	12 (5.2)	12 (5.0)	1 (1.1)	-	1 (0.7)

Data are presented as *n* (%)

see Table 6. The longest period of sustained inflammation was a nonserious, moderate vitritis in a lenadogene nolparvovec eye that lasted approximately 3 years.

Most intraocular inflammations of the lenadogene nolparvovec eyes were either not treated (39.4%) or controlled with topical corticosteroid drops alone (42.2%) (Table 8), with a mean duration of treatment of 39.8 days (median 15.0 days). Less often, intraocular inflammation was treated with both topical corticosteroids and systemic oral corticosteroids (13.9%) or with systemic oral corticosteroids alone (4.4%). Over time, the frequency of ocular inflammation events reported with gene therapy gradually decreased from 170 of 238 during the first 6 months (71.4%) to 82 of 234 between 1 and 2 years (35.0%) and to 30 of 206 between 2 and 3 years (14.6%), as did the use of corticosteroids to treat them (Figure 2). Nearly all inflammation events resolved, and a few patients experienced intraocular inflammation that had not resolved at the last available visit (total of 15 events, all in lenadogene nolparvovec eyes, none being severe).

During intraocular inflammation events, mean OIS remained low but numerically higher in lenadogene nolparvovec eyes compared with uninjected/placebo eyes, with mean global OIS for lenadogene nolparvovec eyes of 1.2/16 for anterior chamber inflammation and 1.0/16 for intermediate uveitis (Table 9). In lenadogene nolparvovec eyes, the mean OIS increased from baseline to week 8 post-IVT, then progressively decreased to baseline values.

As noted above, patients in REFLECT all received oral corticosteroids as a peri-treatment for the prevention or reduction of ocular inflammation related to gene therapy, whereas no preventive corticosteroid treatment was used in the REVEAL, RESCUE, and REVERSE studies. With the same dose of lenadogene nolparvovec injected per eye (9×10^{10} vg), the number of eyes with at least one intraocular inflammation was higher in the REVEAL, RESCUE, and REVERSE studies compared with REFLECT: 69 of 82 eyes (84.1%) and 104 of 147 eyes (70.7%), respectively (Table 6).

TABLE 6. Characteristics of Intraocular Inflammation Events – Safety Population

	Lenadogene Nolparvovec Eye				Uninjected/Placebo Eye		
	REVEAL RESCUE REVERSE Dose 9 x 10^{10} vg ($n = 82$)	REFLECT Dose 9 x 10^{10} vg ($n = 147$)	Total Dose 9 x 10^{10} vg ($n = 229$)	All Doses ($n = 238$)	Total Uninjected ($n = 91$)	REFLECT Placebo - Dose 9 x 10^{10} vg ($n = 49$)	All Doses ($n = 140$)
Number (%) of eyes with at least 1 intraocular inflammation AESI	69 (84.1)	104 (70.7)	173 (75.5)	180 (75.6)	8 (8.8)	5 (10.2)	13 (9.3)
Number of intraocular inflammation events	186	231	417	432	13	6	19
Duration of inflammation (days)							
n	177	224	401	415	13	6	19
Mean (SD)	204.5 (249.7)	159.2 (178.7)	179.2 (213.9)	177.9 (212.7)	127.1 (173.8)	166.3 (153.1)	139.5 (164.4)
Median	91.0	98.0	98.0	92.0	62.0	123.0	64.0
Q1-Q3	36.0-288.0	34.0-201.5	35.0-204.0	34.9-204.0	36.0-81.0	30.0-330.0	32.0-155.0
Range	7.0-1335.0	2.0-858.0	2.0-1335.0	2.0-1335.0	15.0-518.0	16.0-376.0	15.0-518.0
Missing data[a]	9	7	16	17	0	0	0
Maximal grade of inflammation							
n	186	231	417	432	13	6	19
Mild	161 (86.6)	214 (92.6)	375 (89.9)	390 (90.3)	13 (100)	6 (100)	19 (100)
Moderate	21 (11.3)	17 (7.4)	38 (9.1)	38 (8.8)	-	-	-
Severe	4 (2.2)	0 (0.0)	4 (1.0)	4 (0.9)	-	-	-
Localization of inflammation							
n	186	231	417	432	13	6	19
Anterior uveitis	114 (61.3)	135 (58.4)	249 (59.7)	254 (58.8)	11 (84.6)	4 (66.7)	15 (78.9)
Intermediate uveitis	71 (38.2)	93 (40.3)	164 (39.3)	174 (40.3)	2 (15.4)	2 (33.3)	4 (21.1)
Non-specified eye inflammation	1 (0.5)	0 (0.0)	1 (0.2)	1 (0.2)	-	-	-
Posterior uveitis	0 (0.0)	3 (1.3)	3 (0.7)	3 (0.7)	-	-	-

Data are presented as *n* (%), unless otherwise stated

AESI = adverse event of special interest.

[a]Duration of inflammation is missing in a total of 17 eyes as no end dates were recorded in the database (includes 16 eyes with ongoing inflammation [1 eye recovering and 15 eyes not recovered] and 1 eye reported as recovered with no end date).

TABLE 7. Timing of Occurrence of Intraocular Inflammation – By Treatment Arm and Globally – Ongoing and New Intraocular Inflammation Events Over Time – Safety Population

	Bilateral Lenadogene Nolparvovec (REFLECT) ($n = 49$)		Unilateral Lenadogene Nolparvovec (Placebo Contralateral Eye) (REFLECT) ($n = 49$)		Unilateral Lenadogene Nolparvovec (Uninjected Contralateral Eye) (REVEAL, RESCUE, REVERSE, RESTORE) ($n = 91$)			
	First Affected Eye Lenadogene Nolparvovec ($n = 49$) Dose 9×10^{10} vg	Second/Not Yet Affected Eye Lenadogene Nolparvovec ($n = 49$) Dose 9×10^{10} vg	First Affected Eye Lenadogene Nolparvovec ($n = 49$) Dose 9×10^{10} vg	Second/Not Yet Affected Eye Placebo ($n = 49$)	Eye Lenadogene Nolparvovec ($n = 91$)	Eye Uninjected ($n = 91$)	Total All Eyes Treated ($n = 180$)	Total All Doses ($n = 378$)
Whatever the occurrence								
Number (%) eyes with at least 1 intraocular inflammation	35 (71.4)	35 (71.4)	34 (69.4)	5 (10.2)	76 (83.5)	8 (8.8)	180 (75.6)	193 (51.1)
Number of intraocular inflammations	74	79	78	6	201	13	432	451
Time of occurrence (in months)								
n	74	79	78	6	201	13	432	451
Mean (SD)	3.1 (3.9)	3.4 (4.3)	3.6 (3.9)	8.2 (7.7)	4.0 (5.9)	10.8 (11.0)	3.7 (5.0)	3.9 (5.4)
Median	1.9	1.9	1.9	5.3	1.8	5.7	1.9	1.9
Range	0.1-23.3	0.1-23.3	0.1-18.0	1.7-17.8	0.0-35.9	0.5-35.9	0.0-35.9	0.0-35.9
Between 1 and 2 years post-treatment								
Number (%) eyes with at least one intraocular inflammation between 1 and 2 years	2 (4.1)	3 (6.1)	5 (10.2)	2 (4.1)	6 (6.6)	1 (1.1)	16 (6.7)	19 (5.0)
Number of new intraocular inflammations occurring between 1 and 2 years	3	4	6	2	11	4	24	30

(*continued on next page*)

TABLE 7. (*continued*)

	Bilateral Lenadogene Nolparvovec (REFLECT) ($n = 49$)		Unilateral Lenadogene Nolparvovec (Placebo Contralateral Eye) (REFLECT) ($n = 49$)		Unilateral Lenadogene Nolparvovec (Uninjected Contralateral Eye) (REVEAL, RESCUE, REVERSE, RESTORE) ($n = 91$)			
	First Affected Eye Lenadogene Nolparvovec ($n = 49$) Dose 9×10^{10} vg	Second/Not Yet Affected Eye Lenadogene Nolparvovec ($n = 49$) Dose 9×10^{10} vg	First Affected Eye Lenadogene Nolparvovec ($n = 49$) Dose 9×10^{10} vg	Second/Not Yet Affected Eye Placebo ($n = 49$)	Eye Lenadogene Nolparvovec ($n = 91$)	Eye Uninjected ($n = 91$)	Total All Eyes Treated ($n = 180$)	Total All Doses ($n = 378$)
Time of occurrence (in months)								
n	3	4	6	2	11	4	24	30
Mean (SD)	17.7 (5.5)	17.3 (4.6)	14.3 (2.6)	17.6 (0.4)	16.9 (1.9)	19.4 (1.5)	16.4 (3.2)	16.9 (3.0)
Median	17.7	17.0	12.8	17.6	16.6	19.1	16.6	17.3
Between 2 and 3 years post-treatment								
Number (%) eyes with at least 1 intraocular inflammation between 2 and 3 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)	1 (1.1)	2 (0.8)	3 (0.8)
Number of new intraocular inflammations occurring between 2 and 3 years	0	0	0	0	4	1	4	5
Time of occurrence (in years)								
n	-	-	-	-	4	1	4	5
Mean (SD)	-	-	-	-	2.6 (0.4)	3.0	2.6 (0.4)	2.7 (0.4)
Median	-	-	-	-	2.7	3.0	2.7	3.0

Data are presented as *n* (%), unless otherwise stated

TABLE 8. Treatments for Adverse Events of Special Interest Related to Intraocular Inflammation – Safety Population

	Lenadogene Nolparvovec Eye		Uninjected/Placebo Eye		
	Dose 9 × 10^{10} vg (n = 229)	All Doses (n = 238)	Total Uninjected (n = 91)	REFLECT Placebo - Dose 9 × 10^{10} vg (n = 49)	All Doses (n = 140)
Number (%) of eyes with at least one intraocular inflammation	**173 (75.5)**	**180 (75.6)**	**8 (8.8)**	**5 (10.2)**	**13 (9.3)**
Treatment used for intraocular inflammation					
n	173	180	8	5	13
Local corticosteroids	76 (43.9)	76 (42.2)	4 (50.0)	-	4 (30.8)
Local and systemic corticosteroids	25 (14.5)	25 (13.9)	-	1 (20.0)	1 (7.7)
None	64 (37.0)	71 (39.4)	4 (50.0)	4 (80.0)	8 (61.5)
Systemic corticosteroids	8 (4.6)	8 (4.4)	-	-	-
Missing data	0	0	0	0	0
Number (%) of inflamed eyes with at least 7 days of corticosteroids treatment	105 (60.7)	105 (58.3)	4 (50.0)	1 (20.0)	5 (38.5)
Number (%) of inflamed eyes with at least 7 days of local corticosteroids treatment	73 (42.2)	73 (40.6)	4 (50.0)	-	4 (30.8)
Number (%) of inflamed eyes with at least 7 days of systemic corticosteroids treatment	8 (4.6)	8 (4.4)	-	-	-
Number (%) of inflamed eyes with at least 7 days of local and systemic corticosteroids treatment	24 (13.9)	24 (13.3)	-	1 (20.0)	1 (7.7)
Duration of treatment (days) for local corticosteroids					
n	471	471	7	5	12
Mean (SD)	39.8 (69.3)	39.8 (69.3)	80.9 (119.5)	11.6 (10.1)	52.0 (95.4)
Median	15.0	15.0	28.0	8.0	21.0
Q1-Q3	7.0-41.0	7.0-41.0	14.0-103.0	5.0-14.0	11.0-32.0
Range	1.0-490.0	1.0-490.0	14.0-343.0	3.0-28.0	3.0-343.0
Missing data	7	7	0	0	0
Duration of treatment (days) for systemic corticosteroids					
n	166	166	-	7	7
Mean (SD)	14.0 (29.4)	14.0 (29.4)	-	12.1 (5.0)	12.1 (5.0)
Median	8.0	8.0	-	10.0	10.0
Q1-Q3	7.0-15.0	7.0-15.0	-	8.0-15.0	8.0-15.0
Range	2.0-373.0	2.0-373.0	-	8.0-21.0	8.0-21.0
Missing data	1	1	-	0	0

Data are presented as *n* (%), unless otherwise stated

Increased Intraocular Pressure

Elevation of IOP, the second AESI type, occurred with a higher incidence in lenadogene nolparvovec-treated eyes compared with uninjected eyes and placebo eyes (25.2%; n = 60 eyes vs 7.7%; n = 7 eyes and 2.0%; n = 1 eye) (Table 3). All IOP increases were mild to moderate in intensity, and none were serious. Most events in lenadogene nolparvovec eyes were considered as unrelated to study treatment or procedure, and others were related to study treatment (14 of 60 eyes, 23.3%) or procedure (15 of 60 eyes, 25.0%) or both (5 of 60 eyes, 8.3%). Episodes of increased IOP either did not require corrective treatment or were treated with topical IOP-lowering agents. The combination of topical and systemic (acetazolamide) treatment occurred in 10% of cases (7 of 68 eyes with elevated IOP). Many increases in IOP resolved without complication (10 events were still ongoing at the last available visit). Over time, the frequency of IOP elevation decreased.

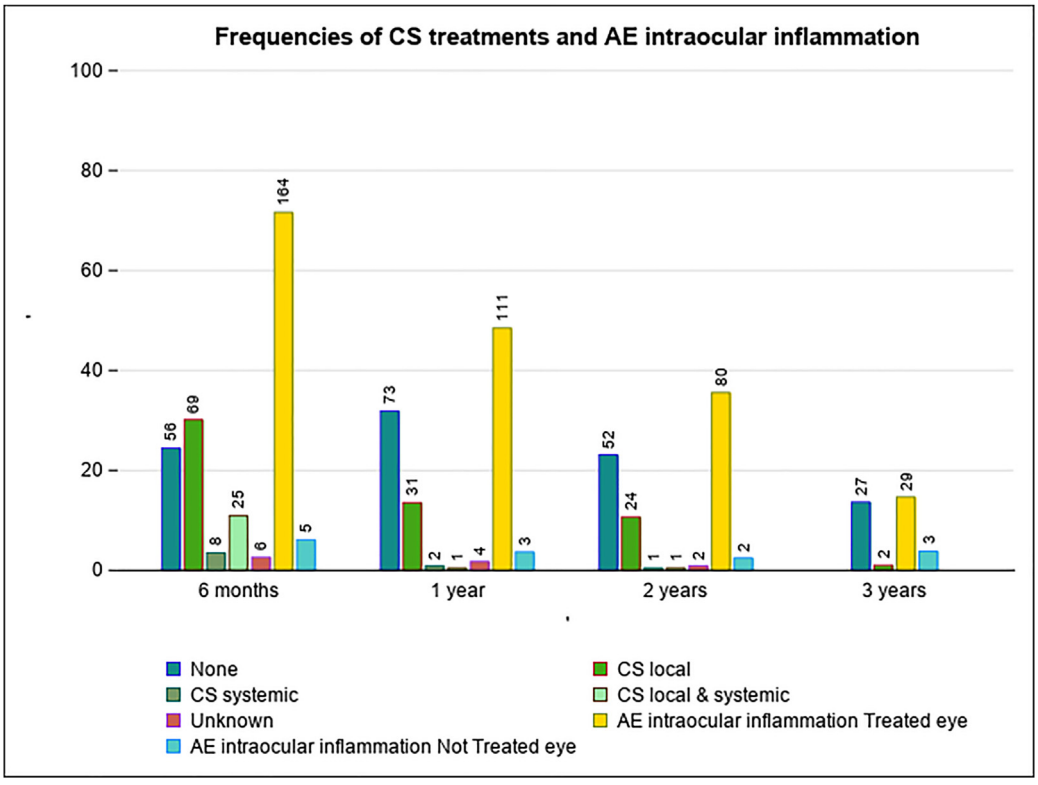

FIGURE 2. Treatment of lenadogene nolparvovec eyes by visit – safety population. The Y axis represents frequencies; the numbers above the bars indicate the numbers of eyes meeting each category of event. AE = adverse event; CS = corticosteroids.

TABLE 9. Mean Ocular Inflammation Scores (OIS) during Anterior and Intermediate Uveitis – Safety Population

	Lenadogene Nolparvovec Eye		Uninjected/Placebo Eye		
	Dose 9 × 10^{10} vg (n = 229)	All Doses (n = 238)	Total Uninjected (n = 91)	REFLECT Placebo - Dose 9 × 10^{10} vg (n = 49)	All Doses (n = 140)
Anterior uveitis					
Number of AESIs	249	254	11	4	15
Mean OIS during the AESIs[a]					
n	228	228	6	4	10
Mean (SD)	1.2 (1.1)	1.2 (1.1)	0.1 (0.2)	0.2 (0.1)	0.1 (0.2)
Median	0.8	0.8	0.0	0.2	0.1
Q1-Q3	0.5-1.6	0.5-1.6	0.0-0.3	0.1-0.3	0.0-0.3
Range	0.0-7.0	0.0-7.0	0.0-0.5	0.0-0.3	0.0-0.5
Missing data	21	26	5	0	5
Intermediate uveitis					
Number of AESIs	164	174	2	2	4
Mean OIS during the AESIs[a]					
n	158	165	2	2	4
Mean (SD)	1.0 (1.2)	1.0 (1.2)	0.5 (0.2)	0.3 (0.1)	0.4 (0.2)
Median	0.6	0.6	0.5	0.3	0.3
Q1-Q3	0.5-1.1	0.5-1.0	0.3-0.7	0.3-0.3	0.3-0.5
Range	0.0-8.5	0.0-8.5	0.3-0.7	0.3-0.3	0.3-0.7
Missing data	6	9	0	0	0

AESI = adverse event of special interest
[a]Maximum OIS = 16.

TABLE 10. Characteristics of Adverse Events of Special Interest (AESI) – By Treatment Arm – Bilateral Lenadogene Nolparvovec; Unilateral Lenadogene Nolparvovec With Placebo injection For Contralateral Eye; Unilateral Lenadogene Nolparvovec With No Injection For Contralateral Eye – Safety Population

	Bilateral Lenadogene Nolparvovec (REFLECT) ($n = 49$)				Unilateral Lenadogene Nolparvovec (Placebo Contralateral Eye) (REFLECT) ($n = 49$)				Unilateral Lenadogene Nolparvovec (Uninjected Contralateral Eye) (REVEAL, RESCUE, REVERSE, RESTORE) ($n = 91$)			
	First Affected Eye Lenadogene Nolparvovec		Second/Not Yet Affected Eye Lenadogene Nolparvovec		First Affected Eye Lenadogene Nolparvovec		Second/Not Yet Affected Eye Placebo		Eye Lenadogene Nolparvovec All Doses		Eye Uninjected	
	Dose 9 x 10^{10} vg		Dose 9 × 10^{10} vg		Dose 9 × 10^{10} vg							
	N	E	N	E	N	E	N	E	N	E	N	E
At least 1 ocular AESI	35 (71.4)	83	37 (75.5)	89	34 (69.4)	86	5 (10.2)	8	79 (86.8)	240	12 (13.2)	21
Intraocular inflammation	35 (71.4)	74	35 (71.4)	79	34 (69.4)	78	5 (10.2)	6	76 (83.5)	201	8 (8.8)	13
Anterior uveitis	28 (57.1)	43	24 (49.0)	45	29 (59.2)	47	3 (6.1)	4	59 (64.8)	119	6 (6.6)	11
Intermediate uveitis	26 (53.1)	29	27 (55.1)	33	28 (57.1)	31	2 (4.1)	2	61 (67.0)	81	2 (2.2)	2
Posterior uveitis	2 (4.1)	2	1 (2.0)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Intraocular pressure increase	9 (18.4)	9	10 (20.4)	10	7 (14.3)	8	1 (2.0)	2	34 (37.4)	39	7 (7.7)	8

Data are presented as n (%) for number of eyes with at least one ocular AESI (N) and n for number of events (E)
E: Number of events; N: Number of eyes with at least one ocular AESI
AESI = adverse event of special interest

Mean (SD) IOP values were globally comparable between lenadogene nolparvovec eyes and uninjected/placebo eyes during events of intraocular inflammation: 15.3 (3.4) mmHg and 16.1 (3.7) mmHg. The proportion of patients with at least 1 increase in IOP > 22 mmHg during intraocular inflammation was 43 of 180 (23.9%) for lenadogene nolparvovec eyes and 5 of 13 (38.5%) for uninjected/placebo eyes. At all timepoints, mean IOP values in inflamed eyes were comparable to non-inflamed eyes. Regarding immediate post-injection IOP increases, 8 patients (3.4%) had IOPs > 22 mmHg after the IVT, all of which were transitory, resolving without complications. Two of these patients were part of the REVEAL study, which used a higher injectable lenadogene nolparvovec volume of 180 µL. The 6 other patients experienced elevated IOP following injection of the lenadogene nolparvovec phase 3 presentation of 90 µL.

In REFLECT, bilateral injections of lenadogene nolparvovec were not associated with differences in the frequency, nature, and severity of ocular AEs compared with unilateral injections. The number of eyes with at least 1 ocular AESI was 35 of 49 (71.4%) for first affected and 37 of 49 (75.5%) for second affected lenadogene nolparvovec eyes of bilaterally treated patients (bilateral REFLECT), 34 of 49 (69.4%) and 79 of 91 (86.8%) for lenadogene nolparvovec eyes of unilaterally treated patients (unilateral with placebo contralateral eye [REFLECT] and unilateral with uninjected contralateral eye [REVEAL/RESCUE/REVERSE/RESTORE], respectively) (Table 10).

• **VITAL SIGNS, PHYSICAL FINDINGS, LABORATORY TESTS:** Overall, no clinically relevant changes from baseline of vital signs, physical examination findings, hematology, and biochemistry parameters were reported. Liver function tests did not change over 2 years after the injection of gene therapy (a few patients were tested thereafter).

• **BIO-DISSEMINATION:** Lenadogene nolparvovec was detected in blood at 2 weeks post-treatment for 2 of 39 patients (5.1%) in RESCUE, for none of the 37 patients in REVERSE, and for 2 of 97 tested blood samples (2.1%) in REFLECT. When the *ND4* transgene was detected, amounts were close to the lower limit of quantification. In REVEAL (15 patients), presence of lenadogene nolparvovec in blood was detected in a few patients with levels close to the limit of quantification; all urine samples were negative for the presence of lenadogene nolparvovec; and some tear samples were positive up to 1 week after gene therapy administration, but no sample remained positive 2 weeks after treatment.

• **IMMUNOGENICITY:** Humoral response against rAAV2/2 vector was assessed by the anti-AAV2 NAbs measured in the serum of patients. After lenadogene nolparvovec injection, a transient mild increase in serum NAbs titers was

reported in patients of the REVEAL study. This immune response was not dose dependent. In RESCUE and REVERSE, NAb levels in serum increased from week 2 post-injection, peaking at week 24 in RESCUE and week 12 in REVERSE. Thereafter, NAb levels slowly decreased toward baseline, and stabilized between week 48 and week 96 post-injection. In REFLECT, there was an increase in NAb levels in serum, with a peak between 14 and 56 days following injection, followed by a decrease. Cellular immune responses against rAAV2/2 were observed in 2 of 15 patients along the time course of the REVEAL study. In RESCUE and REVERSE studies, the cellular response against rAAV2/2 was negative for all but 1 patient and all but 2 patients, respectively, but less than half of the samples were evaluable. In REFLECT, a positive cellular immune response was detected in 11 of 90 patients, which tended to occur between 14 and 56 days after treatment.

For both humoral and cellular immune responses, no relevant differences were observed between unilaterally and bilaterally treated patients.

DISCUSSION

The safety population of these 5 pooled clinical studies comprised 189 LHON patients with the m.11778G>A-ND4 mutation who received single unilateral or bilateral IVT of lenadogene nolparvovec. Almost all of them were treated with a dose of 9×10^{10} vg. This sizable sample of the LHON population was globally representative of the classic clinical presentation of the disease, including young adults with a male predominance.[5] Most patients presented with bilateral visual impairment and a duration of vision loss within 1 year. Due to different inclusion criteria, 10 patients from the REVEAL study were chronic patients with vision loss lasting for several years.

Most systemic events were of mild intensity, and most reported events were common events such as headache. Systemic AEs were exceptionally considered to be related to lenadogene nolparvovec and rarely assessed as related to the study procedure. None of these events were serious. In total, 4 patients died, but their death was unrelated to the study treatment or procedure. Across the studies, few serious neurological events occurred but were assessed as unrelated to study treatment or procedure. Most of them corresponded to neurological disorders described in the literature to be associated with LHON.[25-27] Regarding the patient developing a glioblastoma, the tumor excision tissue analyses showed the absence of lenadogene nolparvovec, indicating that tumor occurrence was unrelated to the gene therapy.[28] No patients discontinued the study due to a systemic AE. The absence of systemic issues related to lenadogene nolparvovec is mainly supported by the limited biodissemination of the product. It was observed in all clinical studies that gene therapy shedding was negligible and transient in the blood, not detected in the urine, and limited and of short duration in patient tears. Of note, the few positive results of bio-dissemination from REVEAL were potentially due to concomitant cytomegalovirus infection and not necessarily from the presence of lenadogene nolparvovec in blood.[20] Indeed, the detection method used in that study targeted the cytomegalovirus promoter of the vector and not the *ND4* transgene as in the later studies.[20] Furthermore, the general humoral and cellular immune response was limited, probably due to a low and transient systemic exposure to the vector following IVT, confirming that the eyes are immuno-privileged.

Most ocular AEs were of mild intensity and no ocular AEs led to study discontinuation. Over the entire program, there was 1 ocular SAE (retinal tear) that occurred in an uninjected eye. The 2 ocular AESI types consisted of intraocular inflammation and IOP increase. Intraocular inflammation, frequently reported as related to lenadogene nolparvovec, was mostly mild, as reflected by the low mean global OIS. These local reactions were treated and controlled with topical corticosteroids alone and rarely required oral corticosteroids, even though oral corticosteroids were not administered at the time of gene therapy injection in 4 of the clinical studies. Of note, a proportion of intraocular inflammations were not treated, reflecting the mildness of these events. Intraocular inflammation events occurred almost exclusively as anterior chamber inflammation and intermediate (ie, vitreous) uveitis, very rarely as posterior uveitis (retinal vasculitis). The proportion of eyes with intraocular inflammation progressively decreased over time, along with the associated use of corticosteroid eye drops. Nevertheless, the proportion of eyes with at least 1 intraocular inflammation event was higher in REVEAL, RESCUE, and REVERSE studies, compared with REFLECT, which was the only study that required oral corticosteroid regimen as a peri-treatment for the prevention or reduction of ocular inflammation related to gene therapy. Furthermore, the 4 severe intraocular inflammation events occurred in REVEAL and REVERSE, and none was observed in REFLECT, suggesting that a preventive treatment with oral corticosteroids seems reasonable.

Intraocular inflammation is an expected side effect of lenadogene nolparvovec. In the literature, intraocular inflammation is reported as one of the most common AEs in clinical studies of AAV-mediated ocular gene therapies, irrespective of the route of administration (IVT or subretinal) of the viral vector (AAV2 or AAV8).[14,29-34] Several reports have also documented intraocular inflammatory responses in preclinical studies of IVT or subretinal AAV injections.[33,35-38] Intraocular inflammation following gene therapy is most likely related to viral capsid and/or exogenous genetic material contained within the capsid.[39]

An increase in IOP can be secondary to the intraocular inflammation and/or treatment with topical steroids or, more acutely, to the volume injected at the time of the IVT. The increases in IOP, mostly mild, were either not treated or

manageable with topical lowering agents alone, and rarely required systemic treatment. Rare cases of elevated IOP after IVT were reported with the current lenadogene nolparvovec injection volume (90 µL per injection), all resolving without complications.

Among the most commonly reported ocular AEs related to the study procedure, punctate keratitis and conjunctival hemorrhage occurred at a similar frequency in lenadogene nolparvovec and uninjected/placebo eyes. Punctate keratitis is usually related to the preparation of the procedure with use of antiseptic agents applied on the periocular skin, whereas conjunctival hemorrhage is related to the IVT itself (pressure on the sclera for uninjected eyes and puncture of the sclera for lenadogene nolparvovec/placebo eyes). In clinical practice, these minor local reactions are frequently observed with IVT[14,40,41] and are treated symptomatically (eg, treatment with artificial tear preparations in the case of punctate keratitis).

Similar to the results of this safety analysis, the US team that developed the scAAV2-P1ND4v2 vector described cases of uveitis after a single IVT of their gene therapy.[14,34] Two of 14 *MT-ND4* LHON patients developed asymptomatic mild anterior uveitis that resolved spontaneously 2 months after the injection. Exposure to this AAV2-ND4 vector also triggered the development of NAbs in a patient-dependent manner as an increase in serum NAbs was observed in 3 of 14 participants, including 1 of the 2 patients with uveitis but not the other.[14] On the contrary, no study treatment-related ocular AEs were reported during 9 months of follow-up in 9 ND4-LHON patients who received a single-dose IVT injection of the rAAV2-ND4 vector from the Chinese group.[10] However, the study conditions were different from the current one, with a more intensive preventive corticosteroid regimen consisting of oral prednisolone administered 1 week before and for 8 weeks after gene therapy.[10] Based on the Chinese group experience and the current studies, for which the mean OIS increased from baseline to week 8 post IVT, the preventive oral corticosteroid coverage regimen could be individualized to patients, with extension over 8 weeks after treatment as needed.

Analysis of the pooled safety data has provided an opportunity to examine the difference in safety profiles between unilateral and bilateral injections of lenadogene nolparvovec on a larger scale. In the REFLECT study, systemic and ocular AEs in bilaterally treated patients (49 patients) did not show differences in frequency, nature, or severity compared with AEs from unilaterally treated patients. Additionally, no relevant differences were observed between bilaterally and unilaterally treated patients in terms of biodissemination and immunogenicity.

Regarding the long-term safety of lenadogene nolparvovec, the interim analysis at year 3 of the 5-year follow-up study RESTORE (62 patients) did not identify any safety concerns,[22] nor did the 5-year open-label, dose-escalation study REVEAL (15 patients).[20] The follow-up of 189 *MT-ND4* LHON patients treated with lenadogene nolparvovec confirms the good safety profile of lenadogene nolparvovec over time after injection, with most patients followed for at least 2 years, and more than one-third of patients followed for 3 years post treatment. This is consistent with data published by Yuan and associates[12] showing no systemic or ocular adverse events during the 7-year follow-up of their 8 patients treated with another rAAV2-ND4 gene therapy.

Among the 189 *MT-ND4* LHON patients in the current safety population, 18 children aged 15 to 18 years were included. The safety profile of lenadogene nolparvovec in this pediatric population was similar to the safety profile observed in the overall population. These results are supported by data from 5 pediatric patients affected with LHON who were treated in the expanded access program under investigator-investigational new drug applications in the USA; no significant safety findings were reported in 2 patients aged 13 years and 3 patients aged 14 years who received bilateral IVTs of lenadogene nolparvovec (Donahue SP, Scientific ePoster PO014, Annual Meeting of the American Academy of Ophthalmology 2021). Likewise, the safety profile of lenadogene nolparvovec was also favorable in elderly patients (≥60 years).

This safety review of lenadogene nolparvovec for the treatment of *MT-ND4* LHON patients constitutes the largest cohort of LHON patients studied after a gene therapy treatment. One limitation of this report is related to the reduced sample sizes of the pediatric and elderly populations, which is inherent to the demographic characteristics of this disease.

In conclusion, based on the pooled safety data from 189 *MT-ND4* LHON patients, lenadogene nolparvovec has a good overall safety profile with excellent systemic tolerability, consistent with its limited bio-dissemination. The systemic humoral and cellular immune response is limited, acknowledging the local ocular nature of the immune response. Lenadogene nolparvovec has a good ocular tolerability, characterized by mostly mild ocular side effects, responsive to conventional ophthalmologic treatments. This safety profile is comparable for both bilaterally and unilaterally treated patients.

Funding/Support: GenSight Biologics (Paris, France) participated in the design of the studies, conducting the studies, data collection, data management, data analysis, interpretation of the data, preparation, review, and approval of the manuscript. NJN and VB are supported in part by NIH/NEI core grant P30-EY06360 (Department of Ophthalmology, Emory University School of Medicine) and by NIH/NINDS (RO1NSO89694). PYWM is supported by an Advanced Fellowship Award (NIHR301696) from the UK National Institute of Health Research (NIHR) and a Clinician Scientist Fellowship Award (G1002570) from the UK Medical Research Council (MRC). PYWM also receives funding from Fight for Sight (UK), the Isaac Newton Trust (UK), Moorfields Eye Charity (GR001376), the Addenbrooke's Charitable Trust, the National Eye Research Centre (UK), the International Foundation for Optic Nerve Disease (IFOND), the NIHR as part of the Rare Diseases Translational Research Collaboration, the NIHR Cambridge Biomedical Research Centre (BRC-1215-20014), and the NIHR Biomedical Research Centre based at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. VC is supported by grants from the Italian Ministry of Health (RF-2018-12366703), the Italian Ministry of University and Research (20172T2MHH), and Telethon-Italy (GGP20115). VC is also supported by patients' organizations MITOCON and IFOND, and patients' donations. BPL is supported by grants from the Research Foundation - Flanders, Belgium (Senior Clinical Investigator 1803821N) and the Concerted Research Action of the Special Research Fund Ghent University (BOF20/GOA/023).
Financial Disclosures: CV-C is a consultant for GenSight Biologics (Paris, France) and has received research support from Santhera Pharmaceuticals (Prattel, Switzerland). PY-W-M is a consultant for GenSight Biologics (Paris, France), Stoke Therapeutics (Bedford, UK) and Transine Therapeutics (Cambridge, UK), and has received research support from GenSight Biologics and Santhera Pharmaceuticals (Prattel, Switzerland). NJN is a consultant for GenSight Biologics (Paris, France), Santhera Pharmaceuticals (Prattel, Switzerland), Chiesi (Parma, Italy), Neurophoenix (Paris, France) and Stoke Therapeutics (Bedford, UK); has received research support from GenSight Biologics and Santhera Pharmaceuticals; served on the Data Safety Monitoring Board for Quark NAION study; and is a medical legal consultant. VC is a consultant for GenSight Biologics (Paris, France), Santhera Pharmaceuticals (Prattel, Switzerland), and Stealth BioTherapeutics (Needham, MA, USA) and has received research support from Santhera Pharmaceuticals and Stealth BioTherapeutics. MLM is a consultant for GenSight Biologics (Paris, France) and has received research support from GenSight Biologics. VB is a consultant for GenSight Biologics (Paris, France) and Neurophoenix (Paris, France). PSS is a consultant for GenSight Biologics (Paris, France), Horizon Therapeutics (Deerfield, IL, USA), Invex Therapeutics (Subiaco, Australia), Viridian Therapeutics (Waltham, MA, USA) and Kriya Therapeutics (Redwood City, CA, USA) and has received research support from Santhera Pharmaceuticals (Prattel, Switzerland), GenSight Biologics, Viridian Therapeutics, and Horizon Therapeutics; and is a medical legal consultant. SPD has been a fee-for-service consultant for GenSight Biologics (Paris, France). BPL is a consultant for GenSight Biologics (Paris, France), 4DMT (Emeryville, CA, USA), AAVantgardeBio (Milano, Italy), Akouos (Boston, MA, USA), Atsena Therapeutics (Durham, NC, USA), Bayer (Leverkusen, Germany), Biogen (Paris, France), IVERIC Bio (New-York, NY, USA), MeiraGTx (London, UK)-Janssen Pharmaceuticals (Raritan, NJ, USA), LookoutGTx, Novartis (Basel, Switzerkand), Opus Genetics (Raleigh, NC, USA), Oxurion (Leuven, Belgium), ProQR Therapeutics (Leiden, The Netherlands), Santen (Osaka, Japan), Spark Therapeutics (Philadelphia, PA, USA), REGENXBIO (Rockville, MD, USA), Vedere Bio (Cambridge, UK), ViGeneron (Planegg, Germany), and has received research support from GenSight Biologics, MeiraGTx-Janssen Pharmaceuticals, Novartis and ProQR Therapeutics. AAS is a consultant for Stealth BioTherapeutics (Needham, MA, USA). TK is a consultant for Santhera Pharmaceuticals (Prattel, Switzerland) and GenSight Biologics (Paris, France). RCS is a consultant for GenSight Biologics (Paris, France). RB is a consultant for Horizon Therapeutics (Deerfield, IL, USA), Healthy Directions (Bethesda, MD, USA) and Guardion Health Sciences (Houston, TX, USA) and has received research support from Santhera Pharmaceuticals (Prattel, Switzerland), Regenera Pharma (Ness-Ziona, Israel) and Quark Pharmaceuticals (Newark, CA, USA). MT and MR are employed by GenSight Biologics (Paris, France), the sponsor of these studies. JAS is a cofounder and shareholder of GenSight Biologics (Paris, France) and a patent coauthor on allotopic transport. All authors attest that they meet the current ICMJE criteria for authorship.
Acknowledgments: Medical writing support was provided by Anne-Coline Laurent and Coline Labbé and was funded by GenSight Biologics (Paris, France). Statistical support was provided by Aurore Caumont-Prim (eXYSTAT, Malakoff, France) and was funded by GenSight Biologics (Paris, France).

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 (Berl)*. 2016;132(6):789–806.
2. Carelli V, La Morgia C, Valentino ML, Barboni P, Ross-Cisneros FN, Sadun AA. Retinal ganglion cell neurodegeneration in mitochondrial inherited disorders. *Biochim Biophys Acta BBA - Bioenerg*. 2009;1787(5):518–528.
3. Newman NJ, Yu-Wai-Man P, Biousse V, Carelli V. Understanding the molecular basis and pathogenesis of hereditary optic neuropathies: towards improved diagnosis and management. *Lancet Neurol*. 2022 0(0.
4. 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.
5. 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.
6. EMA. Raxone. European Medicines Agency. Published September 17, 2018. Accessed April 22, 2022. https://www.ema.europa.eu/en/medicines/human/EPAR/raxone.
7. Klopstock T, Yu-Wai-Man P, Dimitriadis K, et al. A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy. *Brain J Neurol*. 2011;134(Pt 9):2677–2686.
8. 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.
9. 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.
10. Wan X, Pei H, jian Zhao M, et al. Efficacy and safety of rAAV2-ND4 treatment for Leber's hereditary optic neuropathy; 2016:21587.
11. Yang S, qi Ma S, Wan X, et al. Long-term outcomes of gene therapy for the treatment of Leber's hereditary optic neuropathy. *EBioMed*. 2016;10:258–268.
12. Yuan J, Zhang Y, Liu H, et al. Seven-year follow-up of gene therapy for Leber's hereditary optic neuropathy. *Ophthalmology*. 2020;127(8):1125–1127.
13. Feuer WJ, Schiffman JC, Davis JL, et al. Gene therapy for Leber hereditary optic neuropathy: initial results. *Ophthalmology*. 2016;123(3):558–570.

14. 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.
15. Newman NJ, Yu-Wai-Man P, Subramanian P, et al. Randomized trial of bilateral gene therapy injection for m.11778G>A MT-ND4 Leber optic neuropathy. *Brain*. 2022 Nov 9:awac421.
16. Gray RE, Law RH, Devenish RJ, Nagley P. Allotopic expression of mitochondrial ATP synthase genes in nucleus of *Saccharomyces cerevisiae*. *Methods Enzymol*. 1996;264:369–389.
17. Cwerman-Thibault H, Augustin S, Lechauve C, et al. Nuclear expression of mitochondrial ND4 leads to the protein assembling in complex I and prevents optic atrophy and visual loss. *Mol Ther Methods Clin Dev*. 2015;2:15003.
18. Liu HL, Yuan JJ, Zhang Y, et al. Factors associated with rapid improvement in visual acuity in patients with Leber's hereditary optic neuropathy after gene therapy. *Acta Ophthalmol (Copenh)*. 2020;98(6):e730–e733.
19. Bouquet C, Vignal Clermont C, Galy A, et al. Immune response and intraocular inflammation in patients with Leber hereditary optic neuropathy treated with intravitreal injection of recombinant adeno-associated virus 2 carrying the ND4 gene. *JAMA Ophthalmol*. 2019;137(4):399–406.
20. Vignal-Clermont C, Girmens JF, Audo I, et al. Safety of intravitreal gene therapy for treatment of subjects with Leber hereditary optic neuropathy due to mutations in the mitochondrial ND4 gene: the REVEAL study. *Biodrugs*. 2021;35(2):201–214.
21. 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.
22. 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.
23. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. *Am J Ophthalmol*. 2005;140(3):509–516.
24. Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmology*. 1985;92(4):467–471.
25. Nikoskelainen EK, Marttila RJ, Huoponen K, et al. Leber's "plus": neurological abnormalities in patients with Leber's hereditary optic neuropathy. *J Neurol Neurosurg Psychiatry*. 1995;59(2):160–164.
26. Hage A, Vignal-Clermont C, Philibert M, Kanav Khanna R, Hage R. *Neurological findings in patients with Leber's hereditary optic neuropathy - NANOS Annual Meeting*. 2019. Poster 158. Accessed April 26, 2022. https://jlb.onlinelibrary.wiley.com/doi/full/10.1189/jlb.1102574?sid=nlm%3Apubmed.
27. Rościszewska-Żukowska I, Bartosik-Psujek H. Optic nerve atrophy and whole and regional brain atrophy in Leber's hereditary optic neuropathy with multiple sclerosis-like disease with m.11778G>A mutation. *Mult Scler Relat Disord*. 2020;42:102071.
28. Newman NJ, Schniederjan M, Mendoza PR, et al. Absence of lenadogene nolparvovec DNA in a brain tumor biopsy from a patient in the REVERSE clinical study, a case report. *BMC Neurol*. 2022;22(1):257.
29. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *Lancet Lond Engl*. 2017;390(10097):849–860.
30. Maguire AM, Simonelli F, Pierce EA, et al. Safety and efficacy of gene transfer for Leber's congenital amaurosis. *N Engl J Med*. 2008;358(21):2240–2248.
31. Cehajic-Kapetanovic J, Xue K, Martinez-Fernandez de la Camara C, et al. Initial results from a first-in-human gene therapy trial on X-linked retinitis pigmentosa caused by mutations in RPGR. *Nat Med*. 2020;26(3):354–359.
32. Cukras C, Wiley HE, Jeffrey BG, et al. Retinal AAV8-RS1 gene therapy for X-linked retinoschisis: initial findings from a phase I/IIa trial by intravitreal delivery. *Mol Ther*. 2018;26(9):2282–2294.
33. Chan YK, Dick AD, Hall SM, Langmann T, Scribner CL, Mansfield BC. Inflammation in viral vector-mediated ocular gene therapy: a review and report from a workshop hosted by the foundation fighting blindness, 9/2020. *Transl Vis Sci Technol*. 2021;10(4):3.
34. 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 Published online March 7S0002-9394(22)00088-5.
35. Koilkonda RD, Yu H, Chou TH, et al. Safety and effects of the vector for the Leber hereditary optic neuropathy gene therapy clinical trial. *JAMA Ophthalmol*. 2014;132(4):409–420.
36. MacLachlan TK, Lukason M, Collins M, et al. Preclinical safety evaluation of AAV2-sFLT01— a gene therapy for age-related macular degeneration. *Mol Ther*. 2011;19(2):326–334.
37. Ye G, Budzynski E, Sonnentag P, et al. Safety and biodistribution evaluation in cynomolgus macaques of rAAV2tYF-CB-hRS1, a recombinant adeno-associated virus vector expressing retinoschisin. *Hum Gene Ther Clin Dev*. 2015 Published online.
38. Ramachandran PS, Lee V, Wei Z, et al. Evaluation of dose and safety of AAV7m8 and AAV8BP2 in the non-human primate retina. *Hum Gene Ther*. 2017;28(2):154–167.
39. Timmers AM, Newmark JA, Turunen HT, et al. Ocular inflammatory response to intravitreal injection of adeno-associated virus vector: relative contribution of genome and capsid. *Hum Gene Ther*. 2020;31(1-2):80–89.
40. Nuzbrokh Y, Kassotis AS, Ragi SD, Jauregui R, Tsang SH. Treatment-emergent adverse events in gene therapy trials for inherited retinal diseases: a narrative review. *Ophthalmol Ther*. 2020;9(4):709–724.
41. Jager RD, Aiello LP, Patel SC, Cunningham ET. Risks of intravitreous injection: a comprehensive review. *Retina*. 2004;24(5):676–698.