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Interim Results from a Multicenter Observational Safety Study of Patients Treated with Voretigene Neparvovec-Rzyl in the United States

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Objective: To assess long-term safety and exploratory ophthalmic outcomes with voretigene neparvovec-rzyl (VN) in US clinical practice.

Design: Prospective, multicenter, observational postauthorization safety study.

Participants: Eighty-seven patients (169 eyes) receiving VN at 10 ocular gene therapy treatment centers.

Methods: Patients ≥12 months old with viable retinal photoreceptors received VN in ≥1 eye. Subretinal delivery followed a 3-port pars plana vitrectomy modified at surgeons' discretion (e.g., automated foot pedal delivery, prebleb injection, cannula cut, and use of dye for visualization).

Main Outcome Measures: Safety outcomes included treatment-emergent adverse events (TEAEs) and occurrence of chorioretinal atrophy (CRA). Exploratory assessments included changes in best-corrected visual acuity (BCVA) and full-field stimulus threshold (FST). Outcomes were analyzed descriptively; relative risk (RR) was estimated for subgroup comparisons.

Results: With a median of 3.7 years of follow up (range, 2.9–4.9), most patients (95%) reported ≥1 TEAE (387 events); 67% procedure related, 9% attributed to VN, and 82% mild. Chorioretinal atrophy, including related terms retinal degeneration and retinal depigmentation, occurred in 24 patients (27%; 45 eyes), typically within 1 year, and was mild (80%) or moderate (20%). The area of CRA was mostly localized to the retinotomy or bleb area, with 40% of eyes with CRA having atrophy outside the bleb area, and highly correlated between fellow eyes ($r = 0.97$; $P < 0.0001$). Chorioretinal atrophy risk was higher with automated foot pedal administration of VN (RR, 5.33; 95% confidence interval [CI], 1.27–22.40) and in patients with myopia (RR, 8.40; 95% CI, 1.16–60.69). At 3 years, treated eyes showed sustained improvements in BCVA (−0.13 logarithm of the minimum angle of resolution) and FST (−1.68 $\log_{10}$ cd·s/m^2). Best-corrected visual acuity and FST were comparable between CRA and non-CRA eyes, although a subset of CRA eyes showed greater FST improvement at most timepoints up to year 3.

Conclusions: This interim analysis supports the long-term safety of VN in a US cohort, consistent with clinical trial results. Chorioretinal atrophy did not seem to diminish sustained functional and anatomical benefits over minimum 3-year follow up. Ongoing data collection will further clarify the occurrence, impact, and risk factors for CRA while continuing to monitor VN safety in clinical practice.

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Inherited retinal diseases are a heterogeneous group of genetic disorders characterized by severe partial or complete vision loss that affect an estimated 2.5 million individuals worldwide.[1,2] Inherited retinal diseases are caused by pathogenic variants identified in more than 270 disease-associated genes.[2] Among the most severe are those caused by biallelic mutations (i.e., pathogenic or likely pathogenic variants) in *RPE65*, which encodes retinoid isomerohydrolase RPE65, a key enzyme in the visual cycle.[3–5] Clinical manifestations of pathogenic biallelic *RPE65* variants include Leber congenital amaurosis, which is associated with profound vision loss in early infancy and an outer retinal degeneration that overlaps with a phenotype known as retinitis pigmentosa, a heterogeneous group of pigmentary retinopathies with typical onset later in life.[6,7]

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Subretinal delivery of human *RPE65* using adeno-associated virus 2 (AAV2)-based vectors in preclinical and early phase clinical trials[8,9] culminated in the development of voretigene neparvovec-rzyl (VN), an AAV2 vector-based gene therapy approved in the United States (2017) and Europe (2018) for patients with confirmed biallelic *RPE65* mutation-associated retinal degenerations.[10,11] This recombinant AAV2 vector is delivered subretinally and carries human *RPE65* with an optimized Kozak sequence under the control of a chicken β-actin promoter and cytomegalovirus enhancer.[12] Voretigene neparvovec-rzyl predominantly transduces retinal pigment epithelium cells, inducing the production of functional retinoid isomerohydrolase, thereby restoring the visual cycle and visual transduction in viable retinal photoreceptors.[12]

Voretigene neparvovec-rzyl was the first gene therapy approved for commercial use based on efficacy and safety results from 2 open-label, phase I trials (NCT00516477 and NCT01208389) and an open-label, randomized, controlled, phase III trial (NCT00999609).[13–15] Long-term follow up of these trials is ongoing (NCT03602820). In addition, postauthorization safety studies (PASSs) are essential to contextualize clinical trial findings and to monitor outcomes in clinical practice. Here, we report interim results with a minimum follow up of nearly 3 years from the PASS of VN in the United States. This is the largest known PASS of patients treated with VN in the United States to date and includes evaluation of post-VN chorioretinal atrophy (CRA), which was not recognized as a potential safety-related event when the pivotal trials were conducted.[16–20]

Methods

Study Design

This ongoing, prospective, multicenter, observational safety study evaluates patients treated with VN as part of routine care across 10 Ocular Gene Therapy Treatment Centers in the United States (ClinicalTrials.gov identifier, NCT03597399). The target enrollment was at least 40 patients, and the 2-year enrollment period closed on March 31, 2020. Each patient will be followed for 5 years after VN administration. Eligible patients were ≥12 months of age and received VN in at least 1 eye. Participation was encouraged for those receiving VN for autosomal recessive *RPE65*-inherited retinal disease. Patients who had received VN in both eyes before enrollment or who participated in a clinical trial by the study sponsor (Spark Therapeutics, Inc) were excluded.

Patients with viable retinal photoreceptors, assessed via OCT, received subretinal VN at the recommended dose of 1.5×10^{11} vector genomes (0.3 mL) per eye. Both eyes were treated sequentially on separate days. Modifications to the surgical administration procedure, such as vitreous stains, viscous fluid injection systems, or periocular injections, were permitted at the discretion of the treating physician. Prophylactic corticosteroids were prescribed (recommended prednisone or equivalent, 1 mg/kg/day up to 40 mg/day for 7 days, with weekly tapering). This manuscript reports an interim analysis of the ongoing PASS using data collected through January 31, 2023 (Fig 1). This analysis was conducted after the enrolled cohort achieved ∼3 years of minimum follow up, permitting evaluation of medium-term safety outcomes and exploratory ophthalmic assessments while longitudinal follow up remains ongoing. The study was approved by the institutional review board at the Children's Hospital Los Angeles. All patients provided written informed consent. The study adheres to the tenets of the Declaration of Helsinki.

Assessments and Outcomes

Study visits after VN administration were scheduled as part of routine care. Study sites collected patient characteristics at enrollment and VN treatment details at the time of administration, including injection dates, volume administered, and number and location of retinotomies. Safety outcomes and exploratory ophthalmic assessments were evaluated at enrollment and at least annually thereafter, with additional data captured when possible during interim visits and contacts with the patient or other treating physicians and caregivers. Because there was no strict schedule for study visits, exploratory ophthalmic evaluations were allocated to timepoint windows based on postinjection study days. Annual long-term follow-up assessments were assigned to sequential, nonoverlapping windows for year 1 (days 1–455, target day 365), year 2 (days 456–911, target day 730), year 3 (days 912–1275, target day 1095), year 4 (days 1276–1641, target day 1460), and year 5 (days 1642+, target day 1825) of follow up. Data were also analyzed cumulatively as the average of all records within cumulative timepoint windows up to month 3 (days 1–90), up to month 6 (days 1–180), up to month 12 (days 1–365), and up to month 24 (days 1–730). For patients with more than one assessment in a timepoint window, the measurement occurring closest to the target date for that window was used; in the case of equidistant assessments, the latest measurement was used. Baseline assessments were the latest measurement before the treatment date.

Safety assessments included all treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and nontreatment-related SAEs. The intensity of any AE or SAE was assessed as mild, moderate, or severe. Adverse events suggestive of retinal atrophy or degeneration required investigators to indicate whether the event met criteria for CRA (also termed retinal degeneration, retinal depigmentation, or injection site atrophy).[10] Chorioretinal atrophy events were classified according to the nomenclature proposed by Bommakanti et al.[16] Investigators documented whether atrophy patterns were retinotomy touchdown, perifoveal/geographic, nummular, mixed, or none. Genotype data were collected for all enrolled patients and summarized as the number of distinct genotypes and variants observed for those with and without CRA. Retinal thickness was assessed among CRA and non-CRA eyes by spectral-domain OCT with no specified method or location (e.g., central subfield thickness).

Exploratory ophthalmic assessments included changes from baseline (before enrollment or VN administration) in best-corrected visual acuity (BCVA) and full-field stimulus threshold (FST) test. As this was a multicenter observational registry, BCVA was obtained according to local standard-of-care procedures. Available numerical BCVA results were converted to the logarithm of the minimum angle of resolution (LogMAR) for quantitative analysis, where a negative change indicates improvement. The measurement standard (e.g., Snellen, ETDRS) was not prespecified; off-chart results not converted to a numerical value by the investigator were available only for qualitative assessments. Full-field stimulus threshold was measured in decibels (dB) using full-field stimulus testing (Diagnosys*FST*, Diagnosys LLC, https://www.diagnosysllc.com/) with white, red, or blue

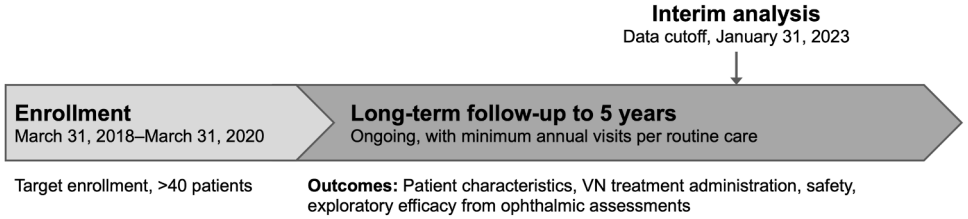


Figure 1. Study design.

light stimuli and converted to $\log_{10}(cd \cdot s/m^2)$ absolute units, consistent with published normative ranges for Diagnosys FST testing.[21] Exploratory ophthalmic assessments were also analyzed in CRA versus non-CRA eyes.

Among eyes with CRA, subgroup analyses based on key variables were performed to explore potential risk factors for CRA, and correlation analysis of estimated atrophic area between fellow eyes was conducted. The subgroup analyses evaluated the relative risk (RR) of CRA with 95% confidence intervals (CIs), where feasible given available sample sizes, for age group (<10 vs. ≥10 years); sex (male vs. female); history of myopia (including high or low myopia, with high myopia defined as refractive error > −6D); use of cannula cut, visualization dye, prebleb, or dynamic intraoperative OCT; presence of intraocular inflammation; number of retinotomies (1 vs. ≥2); injection method (automated foot pedal-controlled versus manual injection); and duration of corticosteroid use.

Statistical Analyses

All outcomes were analyzed descriptively using SAS Version 9.4 (SAS Institute Inc). Potential risk factors for CRA were evaluated using RR, with group comparisons performed using Welch *t* test or Wilcoxon rank-sum test, as appropriate. Correlation of atrophic areas in first- and second-treated eyes was performed using Pearson correlation coefficients with corresponding *P* values. Differences in least squares means for BCVA and FST between eyes with CRA versus eyes without CRA were evaluated using analysis of covariance. No imputation of missing data was performed.

Table 1. Patient Characteristics

Characteristic	Patients (N = 87)
Age at first VN administration, y	
Mean (SD)	16.6 (12.48)
Median	13.0
Range	1–55
Sex, n (%)	
Male	47 (54)
Female	40 (46)
Race, n (%)	
American Indian or Alaska Native	1 (1)
Asian	6 (7)
Black	7 (8)
White	55 (63)
Multiple or other races indicated	10 (11)
Missing	8 (9)
Ethnicity, n (%)	
Hispanic or Latino	10 (11)
Not Hispanic or Latino	76 (87)
Other	1 (1)
Clinical diagnosis, n (%)	
Leber congenital amaurosis, type 2	78 (90)
Retinitis pigmentosa	8 (9)
Severe early onset retinal dystrophy	1 (1)

SD = standard deviation; VN = voretigene neparvovec-rzyl.

Results

Patient Characteristics

A total of 87 patients (174 eyes) were enrolled. Among patients with reported demographics, 54% were male, 87% were not Hispanic or Latino, and 63% were White (Table 1). The mean age at VN administration to the first eye was 16.6 years (standard deviation [SD], 12.5; range, 1–55), and 54 patients (62%) were pediatric (<18 years of age). As of January 31, 2023, the data cutoff date, the median duration of follow up was 3.7 years (range, 2.9–4.9 years). The most common clinical diagnosis was Leber congenital amaurosis type 2, reported in 90% of patients, whereas retinitis pigmentosa was the clinical diagnosis in 9% of patients (Table 1).

Prior gene therapy was included in the history of past ocular procedures for patients who received VN administration in the first eye before their enrollment in the study. For one patient, history of in vivo gene therapy was a different AAV vector (rAAV2-CB-hRPE65; Applied Genetic Technologies Corporation, now Beacon Therapeutics Inc) administered to the patient's first eye as part of their participation in a different clinical trial (Study AGTC-RPE65-002, NCT00749957, Sponsor: Beacon Therapeutics).

Voretigene Neparvovec-rzyl Treatment Administration

A total of 169 eyes (97%) were treated with VN. The majority of eyes (82%) had 1 (60%) or 2 (22%) retinotomy sites (Fig 2A). The mean total injection volume was 297.5 μL (SD, 34.5), corresponding to ∼0.3 mL per eye, in line with the recommended dosing of VN[10] (Fig 2B). Most patients (n = 82; 94%) received bilateral treatment (164 eyes), with a mean interval of 14 days (SD, 8.0; range, 7–43) between injections (Fig 2C). Five patients received unilateral VN.

Modified injection techniques that deviated from those specified in the surgical manual were prevalent. The most common deviations were the use of visualization dyes (117 eyes, 69%), intraoperative OCT (106 eyes, 63%), cutting the cannula tip (80 eyes, 47%), and an automated foot pedal (vs. manual) injection method (89 eyes, 52.7%; Fig 2D–F). Preblebs were reported for 12 eyes (7%), all with balanced salt solution, but one treated eye had "significant unintended air" introduced. This eye also developed CRA, potentially attributable to this complication. Difficulty creating subretinal bleb(s) was reported in 11 treated eyes (7%), and complications were reported in 10 eyes (6%). The complications were retinal breaks repaired by intraoperative endolaser ($n = 5$), retinal hemorrhage ($n = 2$), small lens touch or bite during injection/vitrectomy ($n = 1$), retrobulbar hemorrhage ($n = 1$), and vitreoretinal tuft ($n = 1$). Most were nonserious, mild, and resolved; exceptions were one serious retrobulbar hemorrhage, one retinal break of moderate severity, and unresolved procedural lens bite.

Safety

Nearly all patients experienced ≥1 TEAE (83 of 87, 95.4%; 387 total events). Of these events, 377 of 387 (97.4%) were ocular, affecting 141 eyes in 78 of 87 patients (89.7%). Among all TEAEs, 319 of 387 (82.4%) were mild; 47 of 87 patients (54.0%) had ≥1 mild TEAE. Most were related to the administration procedure (261 of 387 events; 67.4%), which occurred in 69 of 87 patients (79.3%). A summary of overall TEAEs, including any ocular events occurring in ≥2 patients, is provided in Table 2; all TEAEs occurring in all patients are reported in Table S1 (available at www.aaojournal.org). The most common TEAEs (≥10% of patients) were conjunctival hemorrhage (35%), increased intraocular pressure (29%), eye inflammation (23%), lenticular opacities (17%), cataract (17%), eye pain (14%), and conjunctival hyperemia (12%). Chorioretinal atrophy was reported as a TEAE in 20% of patients. In this analysis, CRA was coded using the Medical Dictionary for Regulatory Activities low-level term rather than the preferred term; therefore, this count does not include related preferred terms of retinal degeneration or retinal depigmentation. For aggregate reporting and anatomical classification of all CRA-related events (including related terms), please see the section "Occurrence of chorioretinal atrophy." There were no TEAEs leading to study withdrawal, and no oncologic, hematologic, or immune-related adverse events of special interest (AESIs) were reported. However, one CRA event was classified by the investigator as a neurologic AESI.

There were 3 severe ocular TEAEs affecting 1 eye each in 3 patients, all related to the administration procedure. Lenticular opacities were reported in 1 patient, deemed related to VN and the subretinal delivery procedure by the treating physician, which resolved. Retinal detachment in 1 patient was identified 1 week after injection from an inferior hole that was lasered during the original surgery and reattached with vitrectomy and scleral buckle placement. Unilateral blindness was reported in a 47-year-old patient who experienced unexplained permanent loss of central vision (visual acuity 20/70 at baseline to light perception posttreatment) 6 days after VN administration in the first eye. The patient's FST improved from −1.32 $\log_{10}$[cd·s/m^2] at baseline to −1.5 $\log_{10}$[cd·s/m^2] 3 months posttreatment, but the patient's second eye was not treated because of this AE per the treating physician.

Three ocular SAEs occurred in 1 eye each in 3 patients; these were foveal thinning observed 11 days postinjection that was moderate in severity and remained ongoing; mild retrobulbar hemorrhage resulting from retrobulbar ketamine injection in preparation for vitrectomy that resolved with lateral canthotomy; and a severe rhegmatogenous retinal detachment (described above). In addition, there was 1 nonocular SAE: a first-trimester spontaneous abortion in a partner pregnancy, reported by 1 patient, which was deemed by the treating physician as unrelated to study treatment.

Exploratory Ophthalmic Assessments

Best-Corrected Visual Acuity. Best-corrected visual acuity was assessed in 158 eyes from 81 patients (93%). At baseline, mean (SD) BCVA was 0.90 LogMAR (0.35; $n = 106$ eyes), equivalent to ∼20/160 Snellen, with a range of 1.90 to 0.20 (Fig 3A; shown as patient-level data, averaged over both eyes). In early cumulative posttreatment assessment windows, mean (standard error [SE]) cumulative change from baseline worsened transiently from 0.08 (0.03; $n = 71$ eyes) up to month 3 but returned to baseline by month 6. Mean BCVA change from baseline remained stable from month 6 up to the 24-month cumulative timepoint window (Fig S1, available at www.aaojournal.org).

Long-term annual (noncumulative) BCVA assessments showed mean (SD) values of 0.86 (0.44) at year 1, 0.82 (0.36) at year 2, 0.84 (0.33) at year 3 (minimum follow up), and 0.75 (0.43) at year 4 (Fig 3B). Mean (SE) change from baseline was −0.11 (0.03), −0.12 (0.05), −0.13 (0.06), and −0.17 (0.06), respectively (Fig 3C). The proportion of patients achieving a ≥0.3 LogMAR improvement (averaged across both eyes) increased from 24% at year 1 to 46% by year 4 (Fig 3D).

Full-Field Stimulus Threshold Testing. Full-field stimulus threshold with white light was measured in 112 eyes in 60 patients (69%). At baseline, mean (SD) FST was −1.99 (1.35) log10cd·s/m^2 ($n = 59$ eyes), consistent with reduced sensitivity in this patient population (Fig 4A). In cumulative short-term assessment windows, mean (SD) FST decreased (improved) from baseline to −4.10 (1.63; $n = 39$ eyes) up to month 3 and −4.03 (1.51; n = 50 eyes) up to month 6, corresponding to mean (SE) change from baseline of −1.21 (0.31; $n = 21$ eyes) and −1.25 (0.26; $n = 27$ eyes), respectively. Improvements were maintained at a similar level over the 24-month cumulative window (Fig S2, available at www.aaojournal.org).

On long-term annual (noncumulative) assessments, mean (SE) change from baseline was −1.41 (0.35) at year 1, −1.42 (0.49) at year 2, −1.68 (0.37) at year 3 (minimum follow up), and −1.16 (0.86) at year 4 (Fig 4). Only 1 patient had an FST assessment at year 5, and this patient

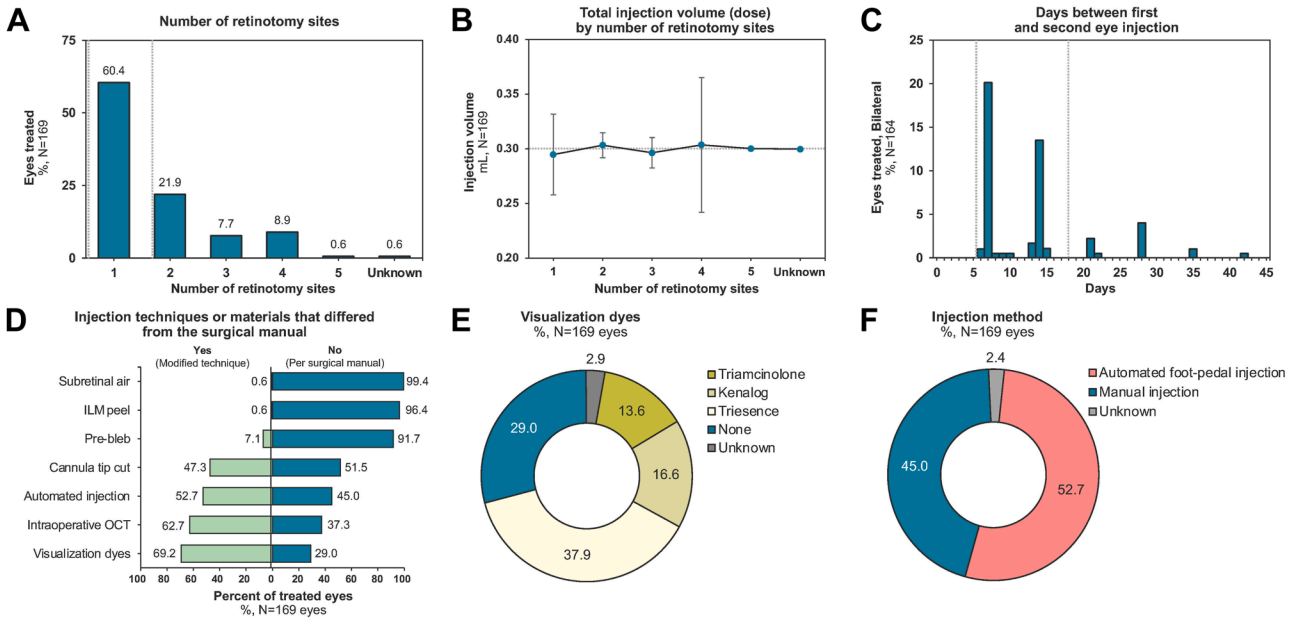


Figure 2. Summary of voretigene neparvovec-rzyl treatment exposure. The number of eyes (and patients, where applicable) treated for surgical administration variables for subretinal injection across the treated population ($N = 169$ eyes). (**A**) Frequency distribution of the number of retinotomy sites. (**B**) Mean total injection volume (dose) stratified by the number of retinotomy sites. Error bars indicate standard deviation. (**C**) Distribution of the time interval (days) between first and second eye injections for patients receiving bilateral treatment ($n = 82$ patients [164 eyes]). (**D**) Prevalence of automated injection technique or materials that differed from the surgical manual (modified technique) vs. adherence to the surgical manual. (**E**) Distribution of specific visualization dyes used. Unknown value includes: Unknown use of any intraoperative visualization dyes ($n = 3$); or, if used, unknown which type of dye was used ($n = 2$). (**F**) Distribution of manual vs. automated injection methods. ILM = internal limiting membrane. Values may not sum to 100% because of rounding.

lacked baseline FST data, precluding analysis of change from baseline for this patient at year 5. The proportion of patients achieving a clinically meaningful improvement (≥1.0-log unit improvement from baseline) ranged between 56% and 64% from year 1 to year 3 (minimum follow up). The percentage of patients achieving at least 0.3 log units (i.e., twofold) improvement ranged from 68% to 91% from year 1 up to year 3. Data were available from 2 patients at year 4, of whom 1 patient maintained ≥1 log improvement.

Blue- and red-light FST assessments demonstrated a similar pattern of substantial, sustained improvement as observed with white-light testing, with mean thresholds improving through year 3 and maintained thereafter (Table S2; available at www.aaojournal.org). Mean (SD) blue-light sensitivity improved from −2.53 (2.78) at baseline to −4.07 (2.92) at year 1 and −5.01 (1.30) at year 3 (minimum follow up). Red-light sensitivity improved from −0.98 (3.18) to −2.57 (1.57) at year 1 and −2.82 (1.11) at year 3 (minimum follow up).

Occurrence of Chorioretinal Atrophy

Chorioretinal atrophy (including related terms retinal degeneration and retinal depigmentation) was reported in 45 of 169 treated eyes (27%) in 24 patients. Cases were mild (80%; 36 of 45 eyes) to moderate (20%; 9 of 45 eyes); none were severe. The mean time to first report was 8.7 months (263.8 days [SD, 233.72 days]). As of the data cutoff, 41 of 45 eyes (91%) were ongoing, 1 had resolved with sequelae, and the outcome was not reported for 3. Bilateral involvement was common; 42 of 45 eyes (93.3%) with CRA were in patients with bilateral CRA who received VN injection in both eyes.

Anatomical distribution of CRA was reported as (categories nonmutually exclusive) present at the injection area including the retinotomy site in 38 of 45 eyes (84%), within the bleb area excluding the retinotomy site in 31 of 45 eyes (69%), and outside the bleb area in 18 of 45 eyes (40%). The anatomical pattern of atrophy was classified as localized exclusively to the retinotomy touchdown site (i.e., retinotomy CRA) in 15 of 45 eyes (33%) (Table 3). Among the remaining 30 eyes (66%) with CRA that were not exclusively related to the retinotomy site (collectively, nonretinotomy CRA), 12 of 30 (40.0%; 26.7% of all CRA eyes) were perifoveal (geographic) and 18 of 30 eyes (60.0%) showed complex patterns combining retinotomy, nummular, perifoveal (geographic), or mixed patterns (Fig 5).

Factors assessed by investigators as possibly contributing to the development of CRA included surgical complications in 7 eyes (16%) and natural disease progression in 9 eyes (20%). In 29 eyes (64%), however, potential contributing factors were unknown or not reported. Intraocular inflammation was observed preceding the onset of atrophy in 9 eyes (20%; vitritis, $n = 5$; anterior uveitis, $n = 4$); inflammation did not occur at or near the atrophy in any of these.

Table 2. Summary of Treatment-Emergent Adverse Events Including Any Ocular Events Occurring in ≥2 Patients

Outcome, n (%)	Patients (N = 87)	Severity*			Relationship*		
		Mild	*Moderate*	*Severe*	*VN*	*Administration Procedure*	*Corticosteroids*
Any TEAE[†]	83 (95.4)	47 (54.0)	33 (37.9)	3 (3.4)	20 (23.0)	69 (79.3)	21 (24.1)
Any serious TEAE	4 (4.6)	2 (50.0)	1 (25.0)	1 (25.0)	0	3 (75.0)	0
Ocular TEAE[‡]	78 (89.7)	48 (61.5)	27 (34.6)	3 (3.8)	20 (25.6)	68 (87.2)	20 (25.6)
Serious ocular TEAE[‡]	3 (3.4)	1 (33.3)	1 (33.3)	1 (33.3)	0	3 (100.0)	0
Eye disorders[†]	77 (88.5)	55 (63.2)	19 (21.8)	3 (3.4)	20 (23.0)	67 (77.0)	3 (3.4)
Conjunctival hemorrhage	30 (34.5)	30 (34.5)	0	0	0	30 (34.5)	0
Eye inflammation	20 (23.0)	20 (23.0)	0	0	3 (3.4)	20 (23.0)	0
Chorioretinal atrophy[§]	17 (19.5)	15 (17.2)	2 (2.3)	0	9 (10.3)	15 (17.2)	0
Cataract[‖]	15 (17.2)	11 (12.6)	4 (4.6)	0	0	11 (12.6)	2 (2.3)
Lenticular opacities	15 (17.2)	13 (14.9)	1 (1.1)	1 (1.1)	0	15 (17.2)	0
Eye pain	12 (13.8)	9 (10.3)	3 (3.4)	0	0	11 (12.6)	0
Conjunctival hyperemia	10 (11.5)	10 (11.5)	0	0	0	8 (9.2)	0
Vitreous opacities	8 (9.2)	8 (9.2)	0	0	5 (5.7)	3 (3.4)	0
Retinal tear	7 (8.0)	6 (6.9)	1 (1.1)	0	0	6 (6.9)	0
Eye irritation	6 (6.9)	5 (5.7)	1 (1.1)	0	0	6 (6.9)	0
Eyelid ptosis	5 (5.7)	5 (5.7)	0	0	0	5 (5.7)	0
Retinal depigmentation	5 (5.7)	2 (2.3)	3 (3.4)	0	3 (3.4)	2 (2.3)	0
Foveal degeneration	4 (4.6)	0	4 (4.6)	0	2 (2.3)	3 (3.4)	0
Visual impairment	4 (4.6)	2 (2.3)	2 (2.3)	0	0	1 (1.1)	0
Eye pruritus	3 (3.4)	2 (2.3)	1 (1.1)	0	0	2 (2.3)	0
Eyelid edema	3 (3.4)	3 (3.4)	0	0	0	3 (3.4)	0
Foreign body sensation in eyes	3 (3.4)	3 (3.4)	0	0	0	3 (3.4)	0
Iritis	3 (3.4)	3 (3.4)	0	0	1 (1.1)	2 (2.3)	0
Retinal degeneration	3 (3.4)	2 (2.3)	1 (1.1)	0	1 (1.1)	1 (1.1)	0
Macular fibrosis	2 (2.3)	2 (2.3)	0	0	0	0	0
Posterior capsule opacification	2 (2.3)	2 (2.3)	0	0	0	2 (2.3)	1 (1.1)
Retinal disorder	2 (2.3)	1 (1.1)	1 (1.1)	0	0	1 (1.1)	0
Retinal hemorrhage	2 (2.3)	2 (2.3)	0	0	0	1 (1.1)	0
Rhegmatogenous retinal detachment	2 (2.3)	0	1 (1.1)	1 (1.1)	0	2 (2.3)	0
Vitreous floaters	2 (2.3)	1 (1.1)	1 (1.1)	0	0	1 (1.1)	0
Vitreous hemorrhage	2 (2.3)	2 (2.3)	0	0	0	2 (2.3)	0
Injury, poisoning, and procedural complications[†]	6 (6.9)	2 (2.3)	4 (4.6)	0	0	2 (2.3)	0
Procedural pain	2 (2.3)	0	2 (2.3)	0	0	1 (1.1)	0
Investigations[†]	25 (28.7)	17 (19.5)	8 (9.2)	0	0	16 (18.4)	17 (19.5)
Intraocular pressure increased	25 (28.7)	17 (19.5)	8 (9.2)	0	0	16 (18.4)	17 (19.5)

TEAE = treatment-emergent adverse event; VN = voretigene neparvovec-rzyl.
*There were a total of 387 events among the 83 patients with ≥1 treatment-emergent adverse event; severity was reported for 381 events (6 events were not reported as mild, moderate, or severe), and relationship to VN, administration procedure, or corticosteroids was reported for 367 events (20 events did not have any relationship reported).
[†]Row denominators for any and ocular TEAEs by severity and relationship are based on the numbers of patients with those events. Row denominators for system organ class (i.e., eye disorders) occurrences by severity and relationship are based on all patients ($N = 87$).
[‡]Ocular TEAEs comprised TEAEs coded to the Medical Dictionary for Regulatory Activities system organ class "eye disorders" as well as ophthalmic histopathology, imaging, and functional diagnostic procedure terms within the system organ class "investigations."
[§]Chorioretinal atrophy was coded as a Medical Dictionary for Regulatory Activities low-level term; all other events used preferred terms. Does not include the related terms retinal degeneration or retinal depigmentation.
[‖]Includes preferred terms of cataract, cataract nuclear, and cataract subcapsular.

In all cases, investigators judged CRA to have no clinically meaningful impact on visual acuity. Among 37 CRA eyes with evaluable microperimetry or visual field testing, 29 (78%) had no clinically meaningful change and 6 (16%) worsened.

Estimated atrophic area assessed in optic disc areas was highly correlated between the first and second-treated eyes ($r = 0.97$; $P < 0.0001$), and eyes with retinotomy-related CRA had a lesser extent of atrophy than eyes with nonretinotomy-related CRA (Fig 5).

Genetic Assessment. Across all participants ($N = 87$), there were 63 *RPE65* variants forming 66 biallelic genotypes. Of these, the 24 patients who experienced CRA harbored 30 variants forming 22 genotypes (33.3% of total participant genotypes) (Fig S3, available at www.aaojournal.org). Only 1 genotype was observed as occurring in >1 patient who

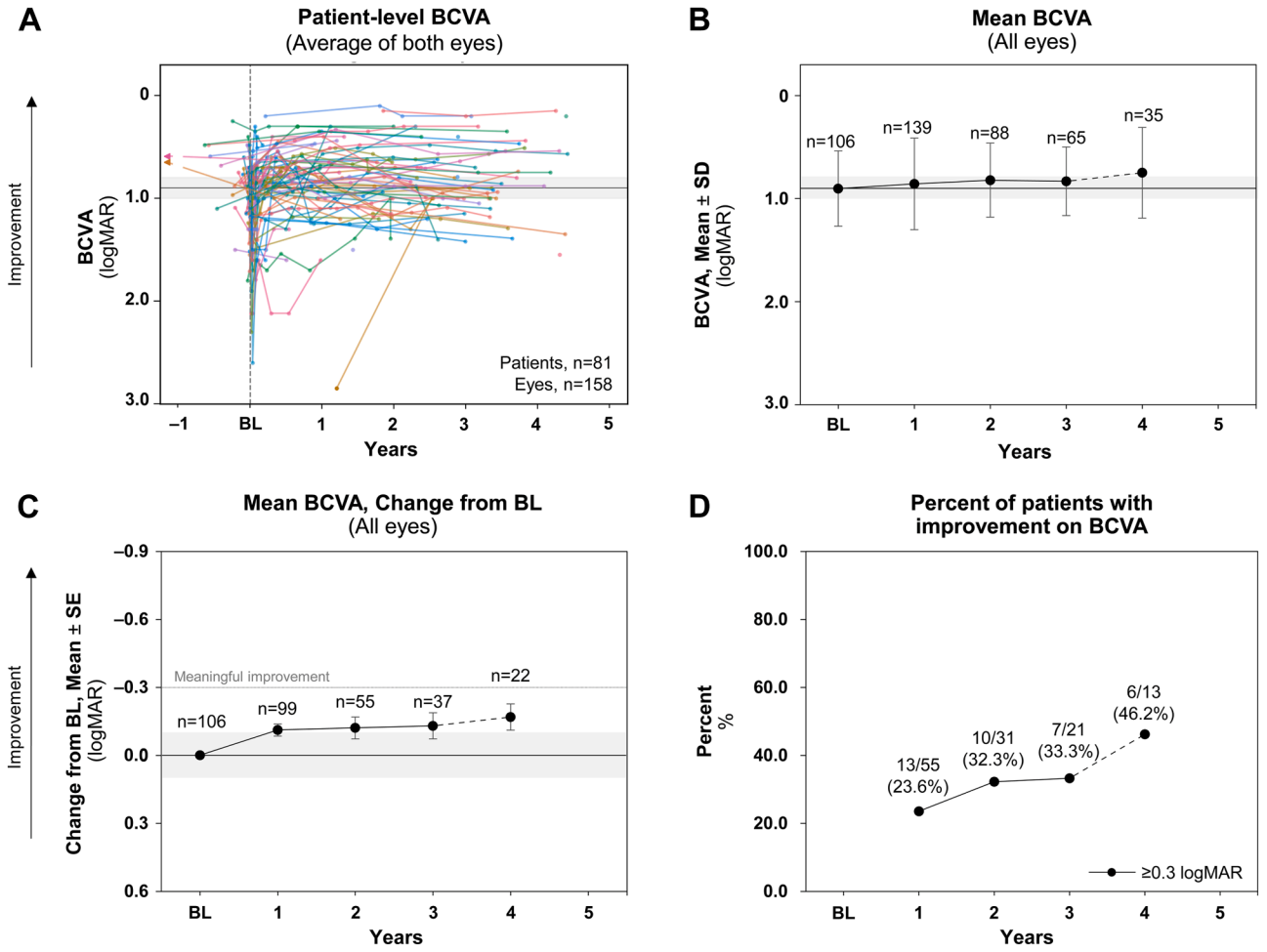


Figure 3. Exploratory long-term best-corrected visual acuity (BCVA) assessments. (**A**) Patient-level BCVA (logarithm of the minimum angle of resolution) assessment values. Data points represent the average value across both eyes. Shaded regions indicate the range of test–retest variability. (**B**) Mean (standard deviation) BCVA assessments through year 5. (**C**) Mean (standard error) BCVA change from baseline assessments through year 5. (**D**) Percentage of patients achieving clinically meaningful BCVA improvement (defined as a decrease of ≥0.3 log of the minimum angle of resolution) up to 5 years. Triangles denote pretreatment baseline assessments collected >1 year before treatment for 2 participants. The vertical dashed line indicates baseline (day 0). The horizontal solid line represents the mean baseline assessment. Dotted lines demarcate assessments beyond the minimum follow up duration (2.9 years) for this interim analysis; data to the right of this line represent a smaller subset of patients. Horizontal dashed lines indicate the threshold for clinically meaningful improvement.

experienced CRA: *RPE65* c.1102T>C (homozygous) was observed in 3 siblings who were enrolled at the same study site (Fig S3). Thus, CRA was observed across diverse *RPE65* genotypes with no recurrence outside a single sibship.

Subgroup Analysis of Risk Ratio. Subgroup analyses showed that the RR of CRA was significantly higher among patients with a history of myopia (RR, 8.40; 95% CI, 1.16–60.69; $P = 0.007$) and with the use of an automated foot pedal rather than manual VN administration (RR, 5.33; 95% CI, 1.27–22.40; $P = 0.008$) (Fig 6). Duration of corticosteroid use was numerically longer for eyes with CRA (mean, 27.6 days) than those without CRA (11.8 days), but the association with CRA was not significant (mean difference, 15.75 days; 95% CI, −12.78 to 44.29; $P = 0.074$).

Ophthalmic Assessments by Occurrence of Chorioretinal Atrophy

Mean BCVA change from baseline was similar between eyes with and without CRA over cumulative time windows up to month 24, whereas mean change in white-light FST was larger (i.e., greater improvement) in eyes with CRA compared with eyes without CRA over the same cumulative time window (Fig 7A, C).

When we compared the year-by-year (noncumulative) change in BCVA between eyes with CRA and eyes without CRA, the model-adjusted least squares mean change from baseline showed no statistically significant difference from year 1 through year 3 (minimum follow up). A slightly greater improvement (−0.24 compared with −0.01) was observed in eyes that developed CRA at year 4 but was not

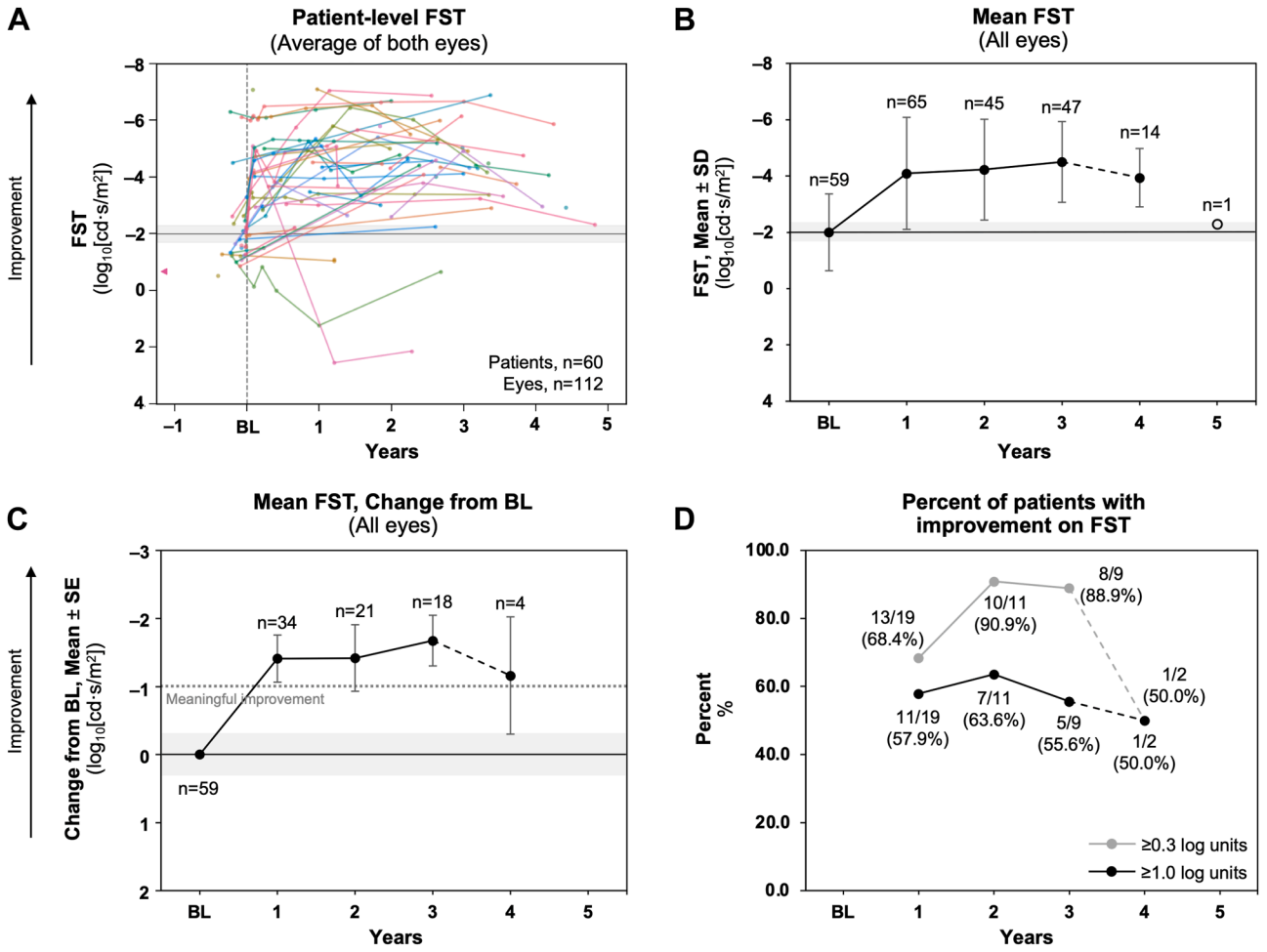


Figure 4. Exploratory long-term full-field light sensitivity threshold assessments. White-light field stimulus threshold (FST) ($\log_{10}$[cd·s/m^2]) patient-level values with mean (standard deviation) and mean (standard error) change from baseline. (**A**) Patient-level white-light FST ($\log_{10}$[cd·s/m^2]) assessment values. Data points represent the average value across both eyes. Shaded regions indicate the range of test–retest variability. (**B**) Mean (standard deviation) FST values through year 5. (**C**) Mean (standard error) change from baseline in FST through year 5. (**D**) Percentage of patients achieving clinically meaningful improvement (defined as an improvement of ≥1.0 log units) or improvement exceeding test–retest variability (defined as an improvement of ≥0.3 log units) in light sensitivity up to 5 years. Triangle denotes pretreatment baseline assessment collected >1 year before treatment for 1 participant. The vertical dashed line indicates the baseline (day 0) timepoint. Dotted lines demarcate assessments beyond the minimum follow-up duration (2.9 years) for this interim analysis; data to the right of this line represent a smaller subset of patients. Horizontal dashed lines indicate the threshold for clinically meaningful improvement.

statistically significant ($n = 22$ eyes; $P = 0.0655$) (Fig 7B). Although changes in FST were numerically greater at year 1 in eyes with CRA compared with eyes with no CRA, they were comparable at year 2, and the difference was not statistically significant up to year 2. However, at year 3, eyes with CRA showed a significantly greater improvement in light sensitivity (lower light threshold) with a least squares mean difference of −2.7 $\log_{10}$(cd·s/m^2) ($P < 0.0001$). There was no statistically significant difference in a comparison of 4 total eyes in year 4 (Fig 7).

Changes in Retinal Thickness. Before VN administration, mean (SD) baseline OCT retinal thickness was 233.1 μm (35.58) across 25 eyes in patients with CRA events and 222.1 μm (70.35) across 70 eyes in patients without CRA events. Mean (SD) changes from baseline in the cumulative assessments of OCT retinal thickness up to month 3 (days 1–90) were 3.5 μm (52.91; $n = 16$) and 9.6 μm (88.73; $n = 31$) among CRA and non-CRA eyes, respectively. Mean (SD) changes up to month 6 (days 1–180) were 3.1 μm (51.19; $n = 16$) and 3.8 μm (69.26; $n = 39$), respectively.

Outcomes in Unilateral Treated Patients. Five participants received treatment in only 1 eye. Outcomes in this subgroup were generally unfavorable, with SAEs or significant visual decline affecting the majority. Three participants had marked losses in visual acuity. One worsened from 0.54 to 1.50 LogMAR, coinciding with an SAE of unilateral blindness; 2 others declined to hand motion vision by year 2. A fourth participant had stable visual acuity but progressive decline in light sensitivity over 2 years; this course was complicated by an SAE of foveal degeneration (foveal thinning) 11 days after treatment. Finally, the fifth participant was previously treated in the fellow eye with a different vector and was the only subject in this group to show evidence of functional improvement

Table 3. Anatomical Patterns of Atrophy and Laterality in Eyes Affected by Chorioretinal Atrophy

Characteristic	Affected Eyes (n = 45)
Injection and CRA laterality (n, %)	
Bilateral CRA, bilateral injection	42 (93.3)
Unilateral CRA, bilateral injection	2 (4.4)
Unilateral CRA, unilateral injection	1 (2.2)
Anatomical patterns of atrophy (n, %)	
Retinotomy only	15 (33.3)
Nonretinotomy	30 (66.7)
Anatomical patterns of nonretinotomy atrophy (n, %)	
Perifoveal	12 (26.7)
Perifoveal/retinotomy	1 (2.2)
Perifoveal/nummular/retinotomy	5 (11.1)
Perifoveal/nummular/retinotomy/mixed	2 (4.4)
Perifoveal/nummular	4 (8.9)
Nummular/retinotomy	3 (6.7)
Mixed	3 (6.7)

CRA = chorioretinal atrophy.
Patients reporting >1 CRA event with the same answer/category to a question are counted only once for that category. A patient who had a CRA event that occurred in both eyes was counted as having 2 events. The number of affected eyes is based on the right/left eye recorded in the verbatim term: OD = right eye, OS = left eye, OU = both eyes (counts as 2 affected eyes). The same eye with multiple events was counted only once for that eye.

after unilateral VN treatment. Although the pretreatment baseline was unavailable, the participant showed progressive improvement from 3 months after treatment (−2.88 log units) to year 3 (−4.32 log units), representing a 1.44 log unit gain in sensitivity over this follow-up period, with stable visual acuity at 0.2 LogMAR. Notably, the participant experienced CRA only in the VN-treated eye.

Discussion

This interim analysis of an observational PASS reports safety outcomes and exploratory ophthalmic assessments with a minimum follow up of nearly 3 years in patients in the US treated with VN. Consistent with previous reports,[12,14,15] most TEAEs were mild or moderate and were generally aligned with complications typical of vitrectomy and subretinal injection (e.g., increased intraocular pressure, cataract, and eye pain),[22–24] except for CRA, which was not considered a typical procedural finding. No TEAEs led to discontinuation, and no oncologic, hematologic, or immune-related AESIs were observed. One event of CRA was classified by the investigator as a neurologic AESI.

Exploratory assessments showed stable or improved BCVA (−0.11 to −0.17 LogMAR over years 1–4; or ∼5–8 letters equivalent) from baseline among evaluable eyes, and clinically meaningful (≥1 $\log_{10}$[cd·s/m^2]) improvements in white light FST for most patients with assessments available. With the exception of cataracts, unresolved vision loss attributable to treatment or procedural complications was rare: 2 eyes experienced permanent central vision loss associated with adverse events (1 eye each of foveal thinning and severe unexplained vision loss) that remained ongoing at the time of analysis; and 2 eyes had a retinal detachment successfully repaired. Collectively, these represent <5% of all treated eyes. In addition, isolated structural findings such as foveal thinning should be interpreted in the context of the known natural history of *RPE65*-associated inherited retinal degeneration, in which foveal abnormalities are frequently observed even at early disease stages[25]; in this study, the reported foveal thinning SAE reflected investigator-assessed intensity rather than quantitative OCT-defined change. Occurrence of CRA did not seem to translate into a measurable loss of visual acuity, and a small subgroup analysis showed greater FST improvement in CRA eyes compared with non-CRA eyes, consistent with prior studies and warranting further investigation. Among the 5 patients who received unilateral treatment, marked visual decline in the treated eye and SAEs were observed; however, the small subset of patients and heterogeneity in characteristics and clinical context preclude firm conclusions, and these findings should be interpreted with caution. It is possible that unfavorable outcomes after first-eye treatment may have influenced the decision not to proceed with second-eye treatment in some cases, although the observational nature of the study and limited available clinical context preclude definitive assessment.

Chorioretinal Atrophy Incidence and Impact on Clinical Outcomes

Chorioretinal atrophy, including atrophy limited to the retinotomy touchdown site, was reported in 45 of 169 eyes in 24 patients (∼27%); nonretinotomy CRA occurred in 30 of 169 eyes in 16 patients (∼18%). The majority of CRA was mild (36 of 45; 80%), with onset in the first year and affecting both treated eyes. Chorioretinal atrophy was frequently localized to the retinotomy or bleb area, but a substantial proportion occurred outside of these regions. No cases were judged by investigators to have a clinically significant impact on visual acuity, and most evaluable eyes showed no microperimetry/visual-field change associated with CRA (29 eyes), with 6 eyes showing worsening. Overall, BCVA outcomes were similar between CRA and non-CRA eyes, whereas FST improvements tended to be greater in CRA eyes. Taken together, despite the identified risks of CRA, the clinical benefit–risk profile for VN remains favorable.

Potential Etiology of Chorioretinal Atrophy

In exploratory analyses, CRA was associated with automated foot pedal delivery (RR, 5.33; 95% CI, 1.27–22.40; P = 0.008) and myopia (RR, 8.40; 95% CI, 1.16–60.69; P = 0.007), with wide CIs reflecting small comparator groups. Moreover, the strong correlation of atrophic areas between fellow eyes (r = 0.97; P < 0.0001) supports both procedural consistency (the same surgeon using the same techniques for both eyes) as well as a biological component.

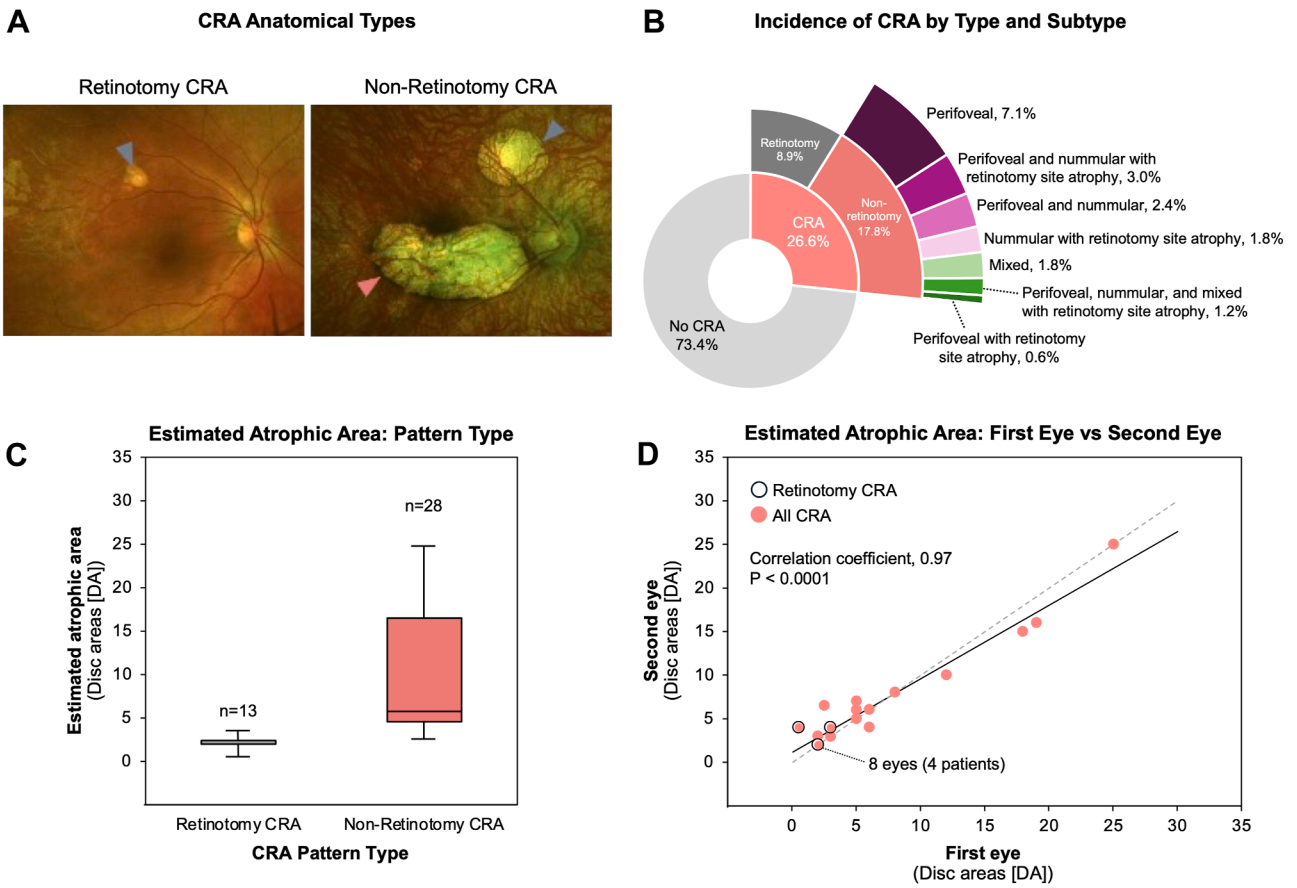


Figure 5. Anatomical patterns and estimated area of atrophy in eyes affected by chorioretinal atrophy (CRA). (**A**) Fundus photography of representative retinotomy CRA (blue arrows) and nonretinotomy CRA (red arrow). (**B**) Incidence of CRA by type and subtype. (**C**) Boxplot of estimated atrophic area in disc areas for retinotomy vs. nonretinotomy CRA. (**D**) Correlation analysis of atrophic area in first-treated vs. second-treated eyes by subtype. Of 24 patients (45 eyes) with CRA, atrophic area values were available for 19 bilateral pairs (19 patients; 38 eyes). In the scatter plot, 16 values are visible because 4 pairs of retinotomy-only eyes had identical area values (2 DA, 2 DA). The remaining 5 patients were excluded because of unilateral CRA ($n = 3$) or inestimable atrophy area ($n = 2$). Patients reporting multiple CRA events within the same category were counted once. Bilateral CRA events were recorded as 2 events. Affected eyes were determined by the recorded laterality (OD, right eye; OS, left eye; OU, both eyes [counted as 2]). Multiple events occurring in the same eye were counted as a single affected eye.

Among patients with CRA	With risk factor, n/N (%)	Reference group, n/N (%)	RR (95% CI)	P value
Age at treatment <10 years (vs ≥10 years)	4/32 (13)	12/55 (22)	0.57 (0.20–1.63)	0.392
Female sex (vs male)	4/40 (10)	12/47 (26)	0.39 (0.14–1.12)	0.095
History of myopia	14/50 (28)	1/30 (3)	**8.40 (1.16–60.69)**	**0.007**
Automated VN administration	12/45 (27)	2/40 (5)	**5.33 (1.27–22.40)**	**0.008**
Cannula cut performed	5/42 (12)	11/45 (24)	0.49 (0.19–1.29)	0.170
Visualization dye used	12/60 (20)	4/26 (15)	1.30 (0.46–3.66)	0.767
Pre-bleb performed	1/7 (14)	15/80 (19)	0.76 (0.12–4.95)	1.000
Dynamic OCT guidance used	11/54 (20)	5/33 (15)	1.34 (0.51–3.53)	0.776
Intraocular inflammation	4/5 (80)	12/19 (63)	1.27 (0.73–2.21)	0.631

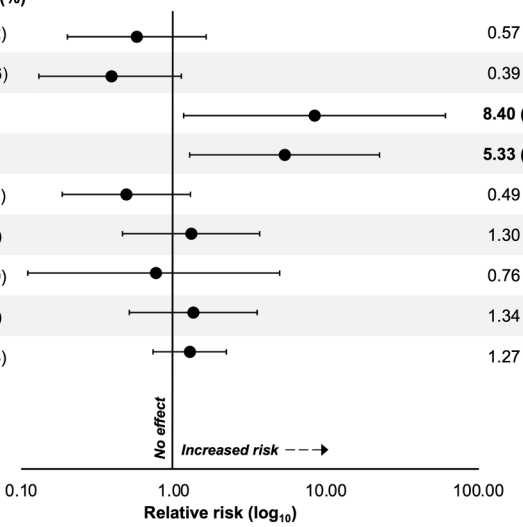


Figure 6. Subgroup analysis of potential risk factors for occurrence of chorioretinal atrophy. Forest plot displaying relative risks for the development of chorioretinal atrophy. Error bars represent confidence intervals; intervals crossing 1.00 indicate no statistically significant effect. *P* values were not corrected for multiple hypothesis testing. VN = voretigene neparvovec-rzyl.

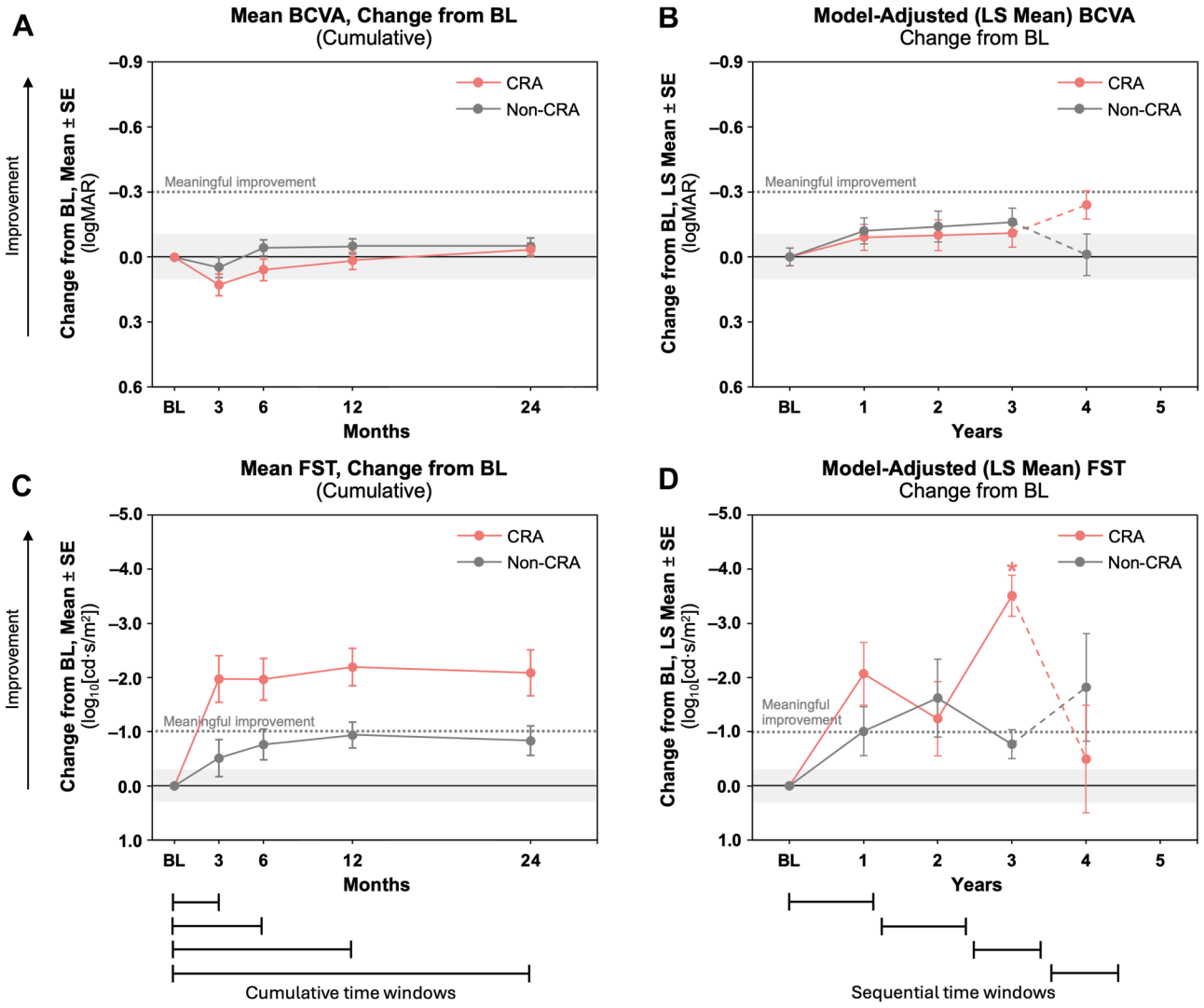


Figure 7. Comparison of changes in best-corrected visual acuity (BCVA) and full-field light stimulus threshold (FST) over early cumulative and annual long-term assessment windows in eyes with chorioretinal atrophy (CRA) vs. eyes without CRA. **A, C**, Mean (standard error) change from baseline in best-corrected visual acuity (**A**) and white light full-field light stimulus threshold (**C**) in eyes with CRA vs. eyes without CRA, calculated cumulatively up to 24 months. **B, D**, Model-adjusted least-squares mean changes from baseline for best-corrected visual acuity (**B**) and full-field light stimulus threshold (**D**). Shaded regions indicate the range of test–retest variability. Horizontal dashed lines represent the threshold for clinically meaningful improvement. LogMAR = logarithm of the minimum angle of resolution.

No specific *RPE65* genotypes were associated with increased CRA risk in this cohort.

Potentially consistent with these findings, eyes that developed CRA may have received a higher effective dose (e.g., greater local vector exposure, stronger biological transduction, or both) driven by delivery dynamics (e.g., injection rate/jet, bleb height, and dwell time) and modified by ocular susceptibility such as myopia. This could produce localized retinal pigment epithelium stress independent of focal inflammation and consistent with bilateral concordance. However, both risks are interpreted as exploratory and potentially confounded by relatively small study size. Other potential factors that may contribute to CRA remain uncertain; hypotheses include vector-related toxicity, immune response, or disease progression. Ongoing monitoring and imaging analyses may help to clarify mechanisms, risk factors, and further clinical implications of CRA.

Evolution in Surgical Techniques

Since VN's approval in 2017, surgical techniques for subretinal delivery have evolved. Nearly two-thirds of cases used triamcinolone to aid vitreous removal and intraoperative OCT to confirm bleb formation, and in almost half of cases, surgeons cut the cannula tip to reduce resistance and facilitate bleb elevation. Automated foot pedal-controlled delivery was used in 52.7% of eyes, enabling

real-time control of injection rate relative to cannula position and bleb size without reliance on a surgical assistant and reflecting a broader trend in subretinal gene therapy. Less common deviations from the original VN surgical manual included use of saline prebleb, internal limiting membrane peel, and subretinal air.

Limitations

The findings of this study should be interpreted in the context of certain limitations. This manuscript reports an interim analysis from a longitudinal PASS designed for postmarketing safety characterization, and although participant follow up is ongoing, the sample size was relatively small, reflecting the rarity of *RPE65*-mediated retinal dystrophy. Of note, the analysis of CRA versus non-CRA eyes had particularly small cohorts with each subsequent year of follow up. Exploratory ophthalmic assessments were only collected in a subset of patients, and there was no standardized schedule or protocol for follow-up evaluations (visual field, FST testing, or imaging), limiting the ability to capture all events or perform more robust statistical analyses. As an observational study, no control group was available for comparison.

Conclusions

This interim analysis of an ongoing PASS supports the safety of VN in US clinical practice. Moreover, benefits observed were durable, with treated eyes demonstrating sustained improvements in BCVA and FST that were broadly comparable with 3- and 4-year visual outcomes previously reported from the phase III trial of VN.[12,15] Chorioretinal atrophy, which emerged as a postauthorization safety observation, occurred in approximately one-quarter of treated eyes but did not seem to impact visual function or retinal structure observed through a minimum follow up of nearly 3 years after VN treatment. Ongoing data collection over 5 years should further clarify the occurrence, clinical impact, and risk factors for CRA while continuing to monitor the safety of VN in clinical practice.

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A.T.: Former employee − Spark Therapeutics Inc.

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Data availability: For eligible studies, qualified researchers may request access to individual patient-level clinical data through a data request platform. At the time of writing, this request platform is Vivli (https://vivli.org/ourmember/roche/). For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://go.roche.com/data_sharing. Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked, due to a potential increase in risk of patient reidentification.

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No animal subjects were used in this study.

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Analysis and interpretation: Nagiel, Chung, Thakre, Savola, Rousso.

Obtained funding: N/A.

Overall responsibility: Nagiel, Russell, Lam, Comander, Aleman, Besirli, Sisk, Yang, Weng, Chung, Thakre, Savola, Rousso.

Abbreviations and Acronyms:
AAV2 = adeno-associated virus 2; **AESI** = adverse event of special interest; **CI** = confidence interval; **CRA** = chorioretinal atrophy; **FST** = full-field stimulus threshold; **LogMAR** = logarithm of the minimum angle of resolution; **PASS** = postauthorization safety study; **RR** = relative risk; **SAE** = serious adverse event; **SD** = standard deviation; **SE** = standard error; **TEAE** = treatment-emergent adverse event; **VN** = voretigene neparvovec-rzyl.

Keywords:
Gene therapy, Inherited retinal disease, Retinal dystrophy, *RPE65*, Voretigene neparvovec-rzyl.

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