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Efficacy, Safety, and Durability of Voretigene Neparvovec-rzyl in *RPE65* Mutation–Associated Inherited Retinal Dystrophy

Results of Phase 1 and 3 Trials

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Purpose: To report the durability of voretigene neparvovec-rzyl (VN) adeno-associated viral vector–based gene therapy for *RPE65* mutation–associated inherited retinal dystrophy (IRD), including results of a phase 1 follow-on study at year 4 and phase 3 study at year 2.

Design: Open-label phase 1 follow-on clinical trial and open-label, randomized, controlled phase 3 clinical trial.

Participants: Forty subjects who received 1.5×10^{11} vector genomes (vg) of VN per eye in at least 1 eye during the trials, including 11 phase 1 follow-on subjects and 29 phase 3 subjects (20 original intervention [OI] and 9 control/intervention [CI]).

Methods: Subretinal injection of VN in the second eye of phase 1 follow-on subjects and in both eyes of phase 3 subjects.

Main Outcome Measures: End points common to the phase 1 and phase 3 studies included change in performance on the Multi-Luminance Mobility Test (MLMT) within the illuminance range evaluated, full-field light sensitivity threshold (FST) testing, and best-corrected visual acuity (BCVA). Safety end points included adverse event reporting, ophthalmic examination, physical examination, and laboratory testing.

Results: Mean (standard deviation) MLMT lux score change was 2.4 (1.3) at 4 years compared with 2.6 (1.6) at 1 year after administration in phase 1 follow-on subjects (n = 8), 1.9 (1.1) at 2 years, and 1.9 (1.0) at 1 year post-administration in OI subjects (n = 20), and 2.1 (1.6) at 1 year post-administration in CI subjects (n = 9). All 3 groups maintained an average improvement in FST, reflecting more than a 2 $\log_{10}$(cd.s/m^2) improvement in light sensitivity at 1 year and subsequent available follow-up visits. The safety profile was consistent with vitrectomy and the subretinal injection procedure, and no deleterious immune responses occurred.

Conclusions: After VN gene augmentation therapy, there was a favorable benefit-to-risk profile with similar improvement demonstrated in navigational ability and light sensitivity among 3 groups of subjects with *RPE65* mutation–associated IRD, a degenerative disease that progresses to complete blindness. The safety profile is consistent with the administration procedure. These data suggest that this effect, which is nearly maximal by 30 days after VN administration, is durable for 4 years, with observation ongoing. *Ophthalmology 2019;126:1273-1285*

See Commentary on page 1286.

Supplemental material available at www.aaojournal.org

Biallelic mutations in the *RPE65* gene, which encodes all-trans retinyl ester isomerase, an enzyme critical to the visual cycle, cause a severe form of rod-mediated inherited retinal dystrophy (IRD) that eventually progresses to complete blindness.[1-4] The spectrum of disease due to autosomal recessive mutations in *RPE65* exhibits a number of common clinical findings, including nyctalopia (night blindness), which is present from early childhood.[2] However, depending on the time of onset, severity, and presenting phenotype, individuals with biallelic *RPE65* mutations may receive a variety of clinical diagnoses, most commonly Leber congenital amaurosis type 2 and retinitis

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pigmentosa type 20.[2] In addition to nyctalopia, *RPE65-mediated* IRD is characterized by progressive loss of visual field (VF) and visual acuity (VA); some cases have earlier onset, more rapid progression, and nystagmus in addition to night blindness and loss of vision.[2] Over time, patients with untreated *RPE65* mutation–associated IRD have near-total loss of the ability to detect light of any intensity.[5] Independent navigation becomes severely limited, leading to impairment of other vision-dependent activities of daily living.[6]

We have evaluated gene augmentation therapy with the recombinant adeno-associated viral vector voretigene neparvovec-rzyl (AAV2-hRPE65v2; VN) in subjects with *RPE65* mutation–associated IRD in 2 open-label phase 1 studies and an open-label, randomized, controlled phase 3 trial.[7-9] The initial dose-escalation phase 1 study evaluated 3 doses of VN using single, unilateral, subretinal injections, including the highest VN dose administered per eye, 1.5×10^{11} vector genomes (vg).[7] In the follow-on phase 1 study, subjects from the initial phase 1 study received 1.5×10^{11} vg of VN in the contralateral, previously uninjected eye, demonstrating the safety and preliminary signs of efficacy of administering VN to the second eye.[8] These phase 1 studies were deemed sufficient to conduct the randomized, controlled phase 3 trial of sequential, bilateral, subretinal administration of VN in subjects with *RPE65* mutation–associated IRD previously untreated with gene therapy.[9] The 2 trials described have demonstrated improved navigational ability, light sensitivity, and VF at 1 year after treatment with VN in subjects with *RPE65* mutation–associated IRD, a population who previously had no approved pharmacologic treatment option and limited retinal implant options. Voretigene neparvovec-rzyl vector design, manufacturing, and formulation, as previously described,[9] were consistent for all trials reported in the current article. On December 19, 2017, the Food and Drug Administration approved VN (LUXTURNA, Spark Therapeutics, Philadelphia, PA) for the treatment of patients with confirmed biallelic *RPE65* mutation–associated retinal dystrophy. Other *RPE65* gene therapy trials, which administered the study drug to only 1 eye per subject using different gene constructs, vector formulations, or surgical approaches, have shown improvements in retinal function but variable duration of effect.[10-14]

In an effort to study the therapeutic durability of VN more comprehensively, we have aggregated data from 2 VN clinical trials. We hypothesized that efficacy and safety results for the phase 3 control group, following crossover to intervention after 1 year of observation, would be similar to those for the original intervention (OI) group, and that gains in functional vision and visual function seen in OI subjects at year 1 would be sustained at year 2. We report the safety and efficacy outcomes for all phase 3 subjects at 2 years, including year 1 results for the control/intervention (CI) group and year 2 results for the OI group. We also report year 4 outcomes for subjects from the phase 1 follow-on study to provide a more comprehensive overview of the efficacy, safety, and durability of response after administration of VN in *RPE65* mutation–associated IRD.

Methods

Study Design and Subjects

The study design and statistical methods, which have been reported, are summarized briefly.[8,9] Each of the reported trials received Institutional Review Board/Ethics Committee approval, which adhered to the tenets of the Declaration of Helsinki. All subjects or their parents/legal guardians gave informed consent, and all related work was Health Insurance Portability and Accountability Act compliant.

The phase 1 follow-on study (ClinicalTrials.gov identifier NCT01208389) enrolled 11 of 12 subjects from the initial dose-escalation phase 1 study of gene augmentation in *RPE65* mutation–associated IRD. Performance on the Multi-Luminance Mobility Test (MLMT) was measured, but because the protocol was not refined over the course of the study, it was not assessed as an end point in the initial dose-escalation phase 1 study, and the dosing regimen was variable (1.5×10^{10}, 4.8×10^{10}, and 1.5×10^{11} vg of VN administered to the first eye); therefore, these data are not included in the assessment of durability for VN. Enrollment criteria included VA more or greater than light perception and sufficient viable retinal cells in the previously uninjected eye. As described in an earlier study report,[8] these subjects received subretinal injection of 1.5×10^{11} vg of VN to the contralateral, previously uninjected eye (i.e., second eye). Subjects were assessed at baseline (≤90 days before day 0 [day of surgical intervention]); on days 1, 2, and 3; at weeks 2 and 4; on days 90 and 180; and then once yearly during years 1 to 5. Per protocol, the first 3 subjects were assessed weekly for 8 weeks to monitor for immunologic responses. All subjects with ocular inflammation at day 3 were also assessed at week 1. Adverse events (AEs) and immune response were monitored, and efficacy data for all subjects evaluable for the MLMT (i.e., those who would have been eligible for the phase 3 trial) were analyzed both individually and in a pooled manner. Figure 1 summarizes the phase 1 follow-on trial design.

The phase 3 study (ClinicalTrials.gov identifier NCT00999609) was an open-label, randomized, controlled trial of gene augmentation in *RPE65* mutation–associated IRD by bilateral subretinal administration of VN conducted at 2 sites in the United States (Children's Hospital of Philadelphia, Philadelphia, PA, and University of Iowa, Iowa City, IA). Subjects who were aged ≥3 years and had a confirmed genetic diagnosis of biallelic *RPE65* gene mutations were eligible for enrollment if both eyes had VA worse than 20/60 or VF <20° in any meridian; they had sufficient viable retinal cells as determined by retinal thickness on spectral domain OCT (>100 μm within the posterior pole), fundus photography, and clinical examination; and they were able to perform the MLMT within the illuminance range evaluated, but were unable to pass the MLMT at 1 lux, the lowest illuminance level tested. Although VA and VF eligibility criteria were different for phase 1 and phase 3, all phase 1 subjects would have qualified for phase 3.

Subjects randomized to the OI group were to receive 1.5×10^{11} vg of VN in each eye. These nonsimultaneous, subretinal injections were given within a protocol-specified range of 12±6 days. Subjects randomized to the control group were to be followed without intervention for at least 1 year after baseline. Subjects in both groups were assessed for retinal and visual function at baseline and days 30, 90, and 180, and 1 year.[9] After 1 year, subjects in the control group who still met all study eligibility criteria received nonsimultaneous subretinal injections of 1.5×10^{11} vg VN in each eye within 18 days (i.e., they crossed over to the CI group). The CI subjects were assessed at the same times as those in the OI group, both in the control year and in the year after VN administration. Continued assessment of both groups is planned yearly for 15 years. Figure 2 summarizes the phase 3 trial design.

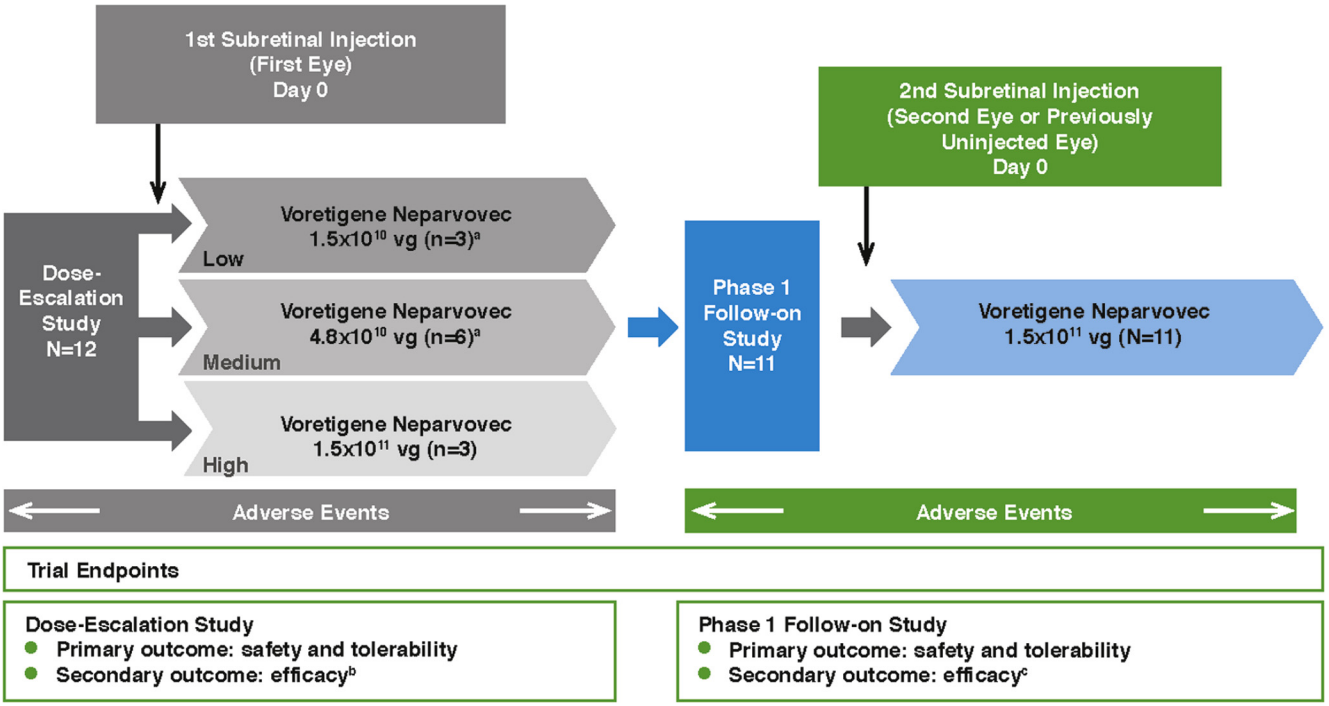

Figure 1. Phase 1 study design. [a]Dose escalation to the next cohort dependent on safety to at least 4 weeks, with a delay of 6 weeks between all subjects. [b]Assessed by change in objective and subjective measures: pupillary light reflex responses, nystagmus testing, standard logarithm of the minimum angle of resolution (logMAR) visual acuity (VA) tests, Goldmann visual fields, full-field light sensitivity threshold (FST) testing, and mobility testing. [c]Assessed on the basis of change in subjective and objective measures (Goldmann visual field tests, FST testing [white, blue, and red stimuli], standard logMAR VA tests, and qualitative pupillary light reflex test, mobility test). vg = vector genomes.

End points common to the phase 1 follow-on (second eye) and phase 3 studies include change in performance on the MLMT within the illuminance range evaluated, full-field light sensitivity threshold (FST) testing, and VA. For the phase 1 follow-on study, all VF testing was performed using Goldmann perimetry with the V4e test stimulus; the more sensitive III4e Goldmann test stimulus was not introduced until the phase 3 study. Therefore, only phase 3 results report this end point. The population for the phase 3 study reported included all subjects who received VN (i.e., the modified intent-to-treat [mITT] population). Other exploratory efficacy end points for both studies have been reported[7-9] and are not included in the current article. For the purposes of efficacy data reported in this article, we define the cohort as all mITT subjects in the phase 3 trial of VN plus all subjects in the phase 1 clinical program of VN who further met the following criteria: (1) participated in the follow-on, contralateral eye study and (2) would have been eligible for the phase 3 trial. Treatment-emergent AEs (TEAEs), physical and ophthalmic examination data, and laboratory results were evaluated in the safety population, defined as all subjects exposed to vector in the phase 1 follow-on and phase 3 studies.

Assessments

Multi-Luminance Mobility Test. The MLMT was developed to address the need for a relevant, reliable, and clinically meaningful measure of functional vision in participants with low vision and nyctalopia. A separate, noninterventional study demonstrated construct and content validity of this end point.[15] Briefly, the 5×10-foot course of the MLMT evaluates a subject's functional vision by measuring the ability to navigate a marked path while avoiding obstacles on or adjacent to the path, negotiating raised steps, and identifying a door at different levels of environmental illuminations. After dark adaptation of 40 minutes, subjects in the phase 1 follow-on and phase 3 studies completed the course with 1 eye patched, then completed a new configuration with the other eye patched, and then again using both eyes. This procedure was repeated at various light levels progressing from lower to higher illuminance levels. Readers masked to study details including treatment group, sequence of visits, and light levels independently graded MLMT video recordings using a standardized, detailed grading rubric that measured both accuracy and time.

In the phase 1 follow-on study, subjects were evaluated for the accuracy and speed at which they completed the MLMT at up to 9 standardized light levels (1, 4, 10, 50, 100, 150, 200, 250, and 400 lux). In refining outcome measures for the phase 3 study, 7 standardized MLMT light levels were used (1, 4, 10, 50, 125, 250, and 400 lux) to distinguish more clearly and discretely subject performance between the testing levels. To facilitate analysis across studies, certain phase 1 light levels were consolidated as follows: 100 and 150 lux (phase 3 = 125 lux) and 200 and 250 lux (phase 3 = 250 lux). Each light level was assigned 1 of 7 discrete lux scores, from 0 to 6. Subjects who were unable to pass at 400 lux were assigned a lux score of −1. Lower light levels corresponded to higher lux scores. Baseline testing established the lowest level of illumination at which each subject could pass the MLMT, with each of the 3 eye-patching conditions.

The MLMT lux scores, as well as change in MLMT performance (change in lux score for the lowest passing light level) relative to baseline at 1-year intervals, are reported for phase 1 follow-on study and phase 3 subjects. Change from baseline in MLMT measures the ability of the intervention to increase functional vision, with a positive change score indicating that a subject has passed the MLMT at a lower light level. All analyses from the phase 1 follow-on and phase 3 studies reported use 7-level scale.

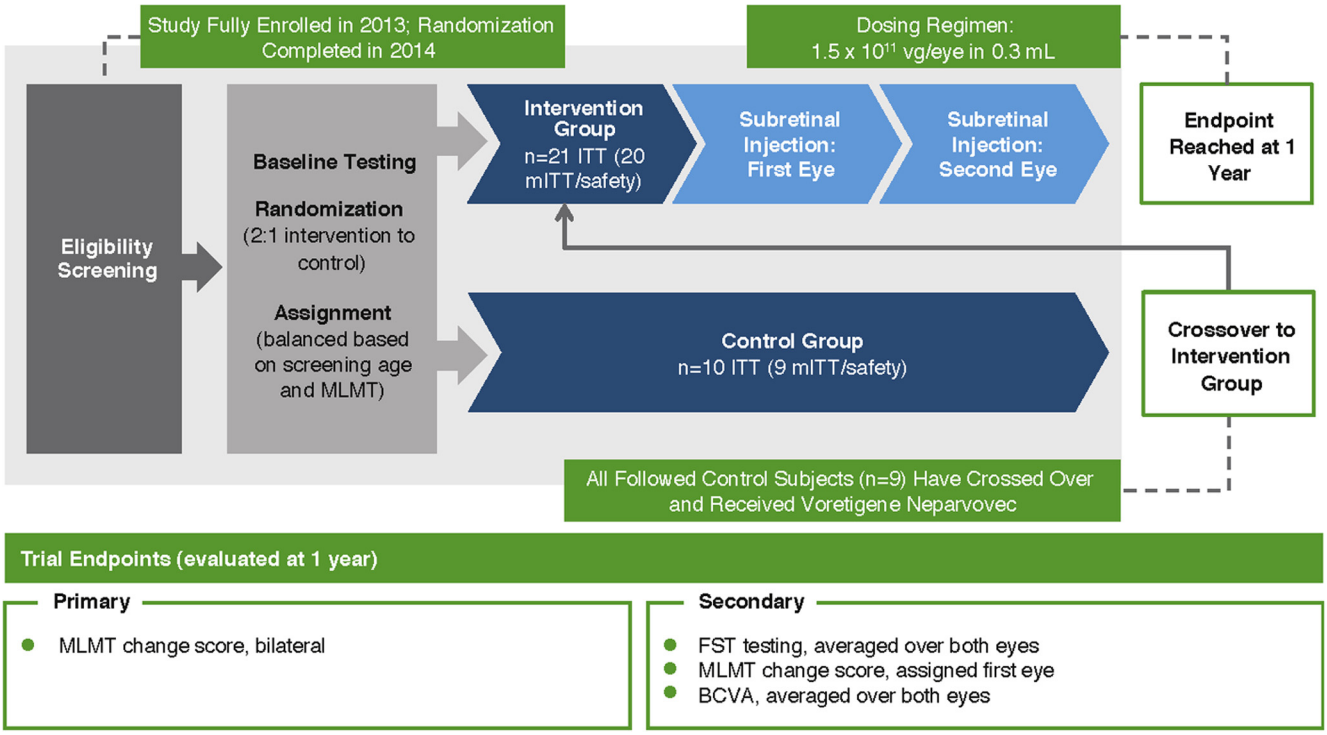

Figure 2. Phase 3 study design (n = 31 ITT, n = 29 mITT/safety). BCVA = best-corrected visual acuity; FST = full-field light sensitivity threshold; ITT = intent-to-treat; mITT = modified intent-to-treat; MLMT = Multi-Luminance Mobility Test; vg = vector genomes. Visual field was an additional, protocol-specified efficacy end point. Reprinted from 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*. 2017;390:849-860, with permission from Elsevier. (http://www.sciencedirect.com/science/journal/Lancet).

Subjects in both studies performed the MLMT with each eye individually (opposite eye patched) and with neither eye patched (bilateral testing condition). This combined report summarizes change in MLMT performance for the phase 1 follow-on study eye (i.e., second eye, which received 1.5×10^{11} vg of VN, of phase 1 subjects) and for the bilateral testing condition (primary efficacy end point) of phase 3 subjects.

Full-Field Light Sensitivity Threshold Testing

Full-field light sensitivity threshold using white light stimuli was performed to measure the lowest illumination perceived, or light sensitivity, over the entire VF. This measure tests the underlying physiologic function of the rod photoreceptors predominantly affected by biallelic *RPE65* mutations. Full-field light sensitivity threshold, which is unaffected by nystagmus, is applicable over a wide range of visual impairment, making it a useful measure for this population.

Visual Acuity

In the phase 1 follow-on and phase 3 studies, best-corrected VA (BCVA) was collected using the scale adapted from Holladay[16] to assign logarithm of the minimum angle of resolution (logMAR) for off-chart vision measurements. In 2013, after the start of the phase 3 study, both the European Medicines Agency and the study's Data and Safety Monitoring Board expressed the opinion that this scale, with assigned logMAR values of 1-log-unit steps for off-chart VA (e.g., between counting fingers and hand motion perception), could overestimate the treatment effect (improvement or reduction in logMAR) for subjects with off-chart measurements at baseline. Both groups recommended post hoc sensitivity analyses for VA using the scale proposed by Lange et al,[17] which reduces the assigned logMAR values for off-chart VA to a 0.3-log-unit step.

In addition, the analysis in the phase 1 follow-on study reported BCVA in the follow-on study eye, whereas the prespecified analysis in the phase 3 study reported BCVA averaged over both eyes. To facilitate VA analysis across the phase 1 follow-on and phase 3 studies, as well as to correct the possible underestimation of bilateral VA with the averaging method used in the phase 3 study (which effectively underweighted the better-seeing eye), the present post hoc analysis reports VA for the first and second eye individually.

Visual Fields

In phase 3 subjects who could see and reliably perform VF testing using the size III4e test stimulus at baseline, this size was used for each subsequent visit. Cumulative VF calculations were conducted across 24 meridians in each eye separately. The outcome measure was the sum of the degrees from central fixation to the point of the isopter intersection for each of the 24 meridians or sum total degrees. Higher sum total degrees indicate a greater area of functional, light-sensitive retina, corresponding to a greater field of vision for the subject. By using this approach, the maximal VF is approximately 1200 to 1400 sum total degrees with the III4e stimulus in individuals without visual impairment.

Statistical Analysis

Observed mean values over time and mean changes from baseline are presented for MLMT, FST, and BCVA. The prespecified primary outcome is the MLMT bilateral change score at 1 year relative to study baseline, and a permutation test *P* value based on a

Wilcoxon rank-sum test was computed from all possible permutations. Stata 13.1 (StataCorp, College Station, TX) was used for statistical analyses in phase 1, and the 2-sided significance level was set at 0.05 for all tests. In phase 3, all figures, summaries, and statistical analyses were created using SAS (version 9.4; SAS Institute, Inc, Cary, NC) and R software (https://www.rproject.org/).

Results

Eleven of 12 subjects from the initial phase 1 study were eligible for and enrolled in the phase 1 follow-on study. Eight of these 11 subjects were considered evaluable for the MLMT, and thus would have met eligibility criteria for the phase 3 study. One non-evaluable subject was able to pass MLMT at 1 lux at baseline, one had atypical performance on MLMT, and one failed MLMT at the highest light level tested at baseline of the phase 1 follow-on study. Efficacy results given are for 8 evaluable subjects, whereas safety results are reported for all 11 subjects.

The phase 3 intent-to-treat (ITT) population included 31 randomized subjects: 21 in the intervention group and 10 in the control group. One subject from each group withdrew or was withdrawn after consent but before the treatment group assignment was known to the subject or the physicians. Neither of these subjects received VN, leaving 20 intervention and 9 control subjects in the mITT and safety analysis populations (Fig 3). We present the safety results for all 40 subjects receiving VN in the phase 1 follow-on and phase 3 studies.

Demographics across the phase 1 follow-on (n = 8) and phase 3 (n = 29) studies are summarized in Table 1. Patients' mean age was somewhat higher for the phase 1 follow-on than for the phase 3 patients because of the lower age limit for inclusion in the phase 3 study.

Efficacy

Multi-Luminance Mobility Test. As shown in Figure 4, mean MLMT lux scores for the phase 1 follow-on and phase 3 studies were similar across the studies. In both studies, mean MLMT lux score improved by the day 30 visit and remained stable for the duration of available data, up to 4 years. Overall, 26 of 37 subjects (70%) passed the MLMT at the lowest illuminance level tested (1 lux) at 1 year, representing the maximum MLMT improvement possible. This included 5 of the 8 evaluable phase 1 follow-on subjects (63%) and 21 of the 29 (72%) phase 3 subjects, including 13 of 20 OI (65%) and 8 of 9 CI (89%) subjects.

Mean (standard deviation [SD]) MLMT change score at year 1 was 2.6 (1.6) for phase 1, 1.9 (1.0) for phase 3 OI, and 2.1 (1.6) for phase 3 CI. Year 2 MLMT change scores were 2.8 (1.5) for phase 1 and 1.9 (1.1) for phase 3 OI; year 3 and year 4 change scores were 2.6 (1.2) and 2.4 (1.3) in phase 1 follow-on subjects, respectively. For comparison, mean MLMT change score at 1 year for phase 3 control subjects, before crossover to the CI group, was 0.2 (1.1), resulting in a mean treatment difference (95% CI) of 1.6 (0.76, 2.5) ($P = 0.004$, mITT); no control subject passed the MLMT at 1 lux in the control year.[9]

Full-Field Light Sensitivity Threshold Testing

Mean white light FST, reported in the follow-on study (second injected) eye for phase 1 subjects and averaged over both eyes for phase 3 subjects, is shown in Figure 5. Overall, for all treatment groups, after vector administration, the gain in FST performance was greater than 1.8 $\log_{10}$ units ($\log_{10}$[cd.s/m^2]) by day 30, and by year 1, improved to 2.3 $\log_{10}$ units, which has remained stable for up to 4 years.

Multi-Luminance Mobility Test and Full-Field Light Sensitivity Threshold Testing

At year 1, most subjects with improvements in MLMT, including all 8 evaluable phase 1 follow-on subjects, 19 of 20 OI subjects (95%) and 8 of 9 CI subjects (89%), also showed improvements in FST. Among subjects with MLMT improvements and nonmissing FST change at year 1, 7 of the 8 evaluable phase 1 follow-on subjects (88%), 13 of the 18 OI subjects (72%), and all 8 CI subjects had FST change of >1 $\log_{10}$ units. All subjects who passed the MLMT at the lowest illuminance level tested (1 lux) at 1 year had an improvement in FST of >1 $\log_{10}$ units; conversely, 25 of the 28 subjects (89%) who had an improvement in FST of >1 $\log_{10}$ units passed the MLMT at 1 lux at 1 year. One OI MLMT responder had missing FST data because of an inability to complete testing at baseline due to attentional limitations (4 years old at study enrollment). Overall, the correlation between change in bilateral MLMT and FST averaged over both eyes was high at year 1 of the phase 3 study, with a Pearson correlation coefficient of -0.71 (Fig S1, available at www.aaojournal.org).

Additional analyses were performed for subjects who improved by 1 light level on the MLMT to assess the clinical impact of this change. In the phase 3 group, 11 treated subjects (8 OI and 3 CI) improved by 1 light level on the MLMT; 7 of these achieved the maximum lux score of 6 or passed at the 1 lux level (i.e., these individuals may have been limited to a change of 1 by a ceiling effect; Fig 6A). As shown in Figure 6B, all subjects administered VN with an MLMT change score of 1 experienced improvements in FST, ranging from approximately 1 to 5 $\log_{10}$ units, with the greatest FST improvement seen in those whose passing score on the MLMT improved from 4 lux to 1 lux. This demonstrates the greater dynamic range of FST and the ceiling effect of the MLMT score at the minimum measurable light level of 1 lux.

During the control year, 3 control subjects (i.e., with no intervention) showed a 1 light level increase on MLMT, and 1 control subject showed a 2 light level increase on MLMT (Fig 6C). Figure 6D illustrates that these untreated control subjects with MLMT change scores ≥ 1 did not improve or actually worsened on FST, demonstrating the specificity of FST for global visual function.

Visual Acuity

The results of BCVA are given in logMAR units, where smaller values indicate better acuity (i.e., less BCVA loss). Off-chart BCVA measurements used Lange adaptations of previously reported scales for assigning logMAR.[17] For the BCVA analyses, a 0.1 improvement in logMAR corresponds to a 5-letter improvement (equivalent to 1 line) on an Early Treatment Diabetic Retinopathy Study standard eye chart. Figure 7 demonstrates mean BCVA results using Lange off-chart acuities. In contrast to the expected rate of BCVA decline over 4 years associated with the natural history of *RPE65* mutation–associated IRD, phase 1 subjects had nearly stable BCVA until year 4, when mean (SD) change from baseline increased to 0.10 (0.21) logMAR (loss of 5 letters) in the phase 1 follow-on study eyes. A phase 1 subject who was included in the evaluable group of 8 had expansion of retinal pigment epithelium depigmentation associated with profound pathologic high myopia, which was accompanied by a decline in BCVA from 0.75 logMAR at baseline to 1.82 logMAR at year 3.

As assessed in this post hoc analysis, year 1 improvements from baseline in BCVA in the first and second eye in the phase 3 OI subjects were minimal (mean [SD]: first eye, -0.21 [0.25] logMAR and second eye, -0.15 [0.19] logMAR; improvement of 11

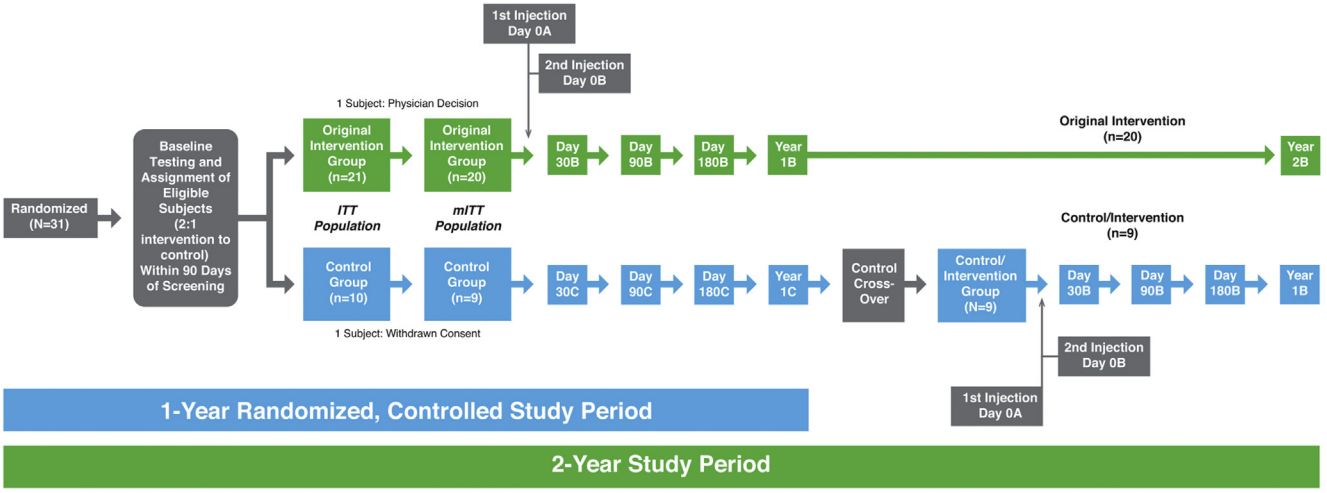

Figure 3. Phase 3 study design. ITT = intent-to-treat; mITT = modified intent-to-treat.

and 8 letters, respectively) and not statistically significant when compared with the control group. The OI year 2 mean (SD) change from baseline was −0.20 (0.27) logMAR (improvement of 10 letters) in the first eye and −0.15 (0.22) logMAR (improvement of 8 letters) in the second eye. Year 1 CI mean (SD) change from baseline was −0.10 (0.21) logMAR (improvement of 5 letters) in the first eye and −0.08 (0.25) logMAR (improvement of 4 letters) in the second eye. One CI subject experienced permanent decrease in foveal function (i.e., >0.3 logMAR worsening, loss of at least 15 letters) in the second eye first measured 30 days after VN administration. The vision loss of this 1 CI subject was associated with corresponding structural changes in the OCT (i.e., greater than expected thinning of the foveal region); the degree of thinning was similar to that seen in rhegmatogenous retinal detachment but not typically seen after the transient bleb created in the subretinal injection procedure.

With the exception of baseline mean VA in the OI first eye, phase 1 mean BCVA was worse than phase 3 mean BCVA at all study visits, including second eye at baseline and first and second eyes at all other visits. This was consistent with several factors: (1) Phase 1 eligibility criteria specified a VA of 20/160 or worse, whereas phase 3 specified VA of 20/60 or worse; (2) the mean age

Table 1. Demographics

Variable	Statistics	Category	Phase 1 Follow-on Study (n = 8)†	Phase 1 Follow-on Study (n = 11)‡	Phase 3 Original Intervention (n = 20)	Phase 3 Control/Intervention (n = 9)	Total* (N = 40)
Age at intervention, yrs	Mean (SD)		19.9 (8.0)	22.8 (10.3)	14.6 (12.0)	15.2 (8.3)	16.8 (11.1)
	Min, max		11, 30	11, 46	4, 44	5, 29	4, 46
Sex	N (%)	Female	3 (38)	5 (45)	12 (60)	6 (67)	23 (57)
		Male	5 (62)	6 (55)	8 (40)	3 (33)	17 (43)
Race	N (%)	White	7 (88)	10 (91)	14 (70)	6 (67)	30 (75)
		Asian	1 (12)	1 (9)	2 (10)	2 (22)	5 (13)
		American Indian or Alaska Native	0	0	2 (10)	1 (11)	3 (8)
		Black or African American	0	0	2 (10)	0	2 (5)
Ethnicity	N (%)	Not Hispanic or Latino	8 (100)	11 (100)	15 (75)	8 (89)	34 (85)
		Hispanic or Latino	0	0	5 (25)	1 (11)	6 (15)
MLMT passing level (phase 3 randomization strata)	N (%)	<125 lux	5 (62)	6 (55)	12 (57)	4 (40)	16 (52)
		≥125 lux	3 (38)	5 (45)	9 (43)	6 (60)	15 (48)

MLMT = Multi-luminance Mobility Test; SD = standard deviation; VN = voretigene neparvovec.
*Total includes the phase 1 safety population, the phase 3 original intervention (OI) population and the phase 3 control/intervention (CI) population.
†Efficacy population; 8 of the 11 subjects who entered the phase 1 follow-on study were evaluable for MLMT, and thus would have met eligibility criteria for the phase 3 study.
‡Safety population: includes all subjects exposed to VN in the phase 1 follow-on study (11 of the 11 patients).

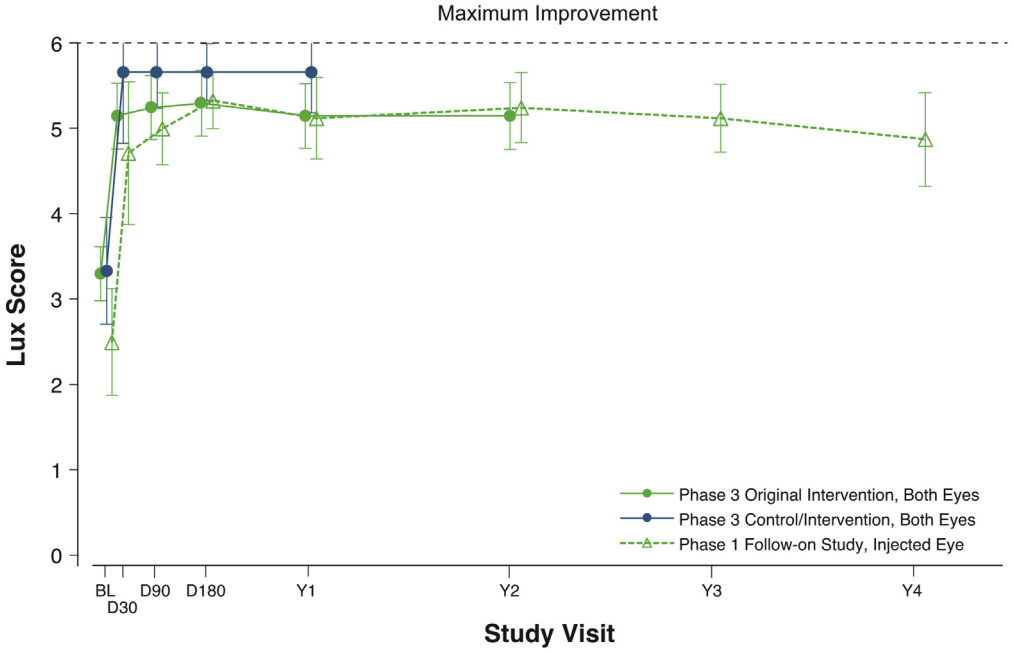

Figure 4. Mean Multi-Luminance Mobility Test (MLMT) lux scores from administration baseline in evaluable phase 1 follow-on subjects (n = 8) and phase 3 subjects (mITT population). Intervals are ±1 standard error. BL = baseline; D = day; mITT = modified intent-to-treat; Y = year.

of the phase 1 subjects was older (phase 1, 19.9 years; phase 3, 14.3 years) and may have affected VA given its natural history in *RPE65* mutation–associated IRD.[18]

Visual Fields

Visual field results from the phase 1 follow-on and phase 3 studies could not be combined or compared because these studies used different testing methods. Furthermore, Goldmann V4e VF data showed large variability from visit to visit in all phase 1 subjects, likely because of the difficulty in performing this test in subjects with low vision, including difficulty of fixation caused by advanced macular disease and nystagmus. Therefore, we present only phase 3 Goldmann VF III4e results.

Overall, phase 3 subjects had a mean (SD) gain from baseline in sum total degrees on Goldmann VF III4e testing of approximately 267 (276) sum total degrees at year 1. The OI group gained 302 (290) sum total degrees, a 92% increase from baseline, at year 1

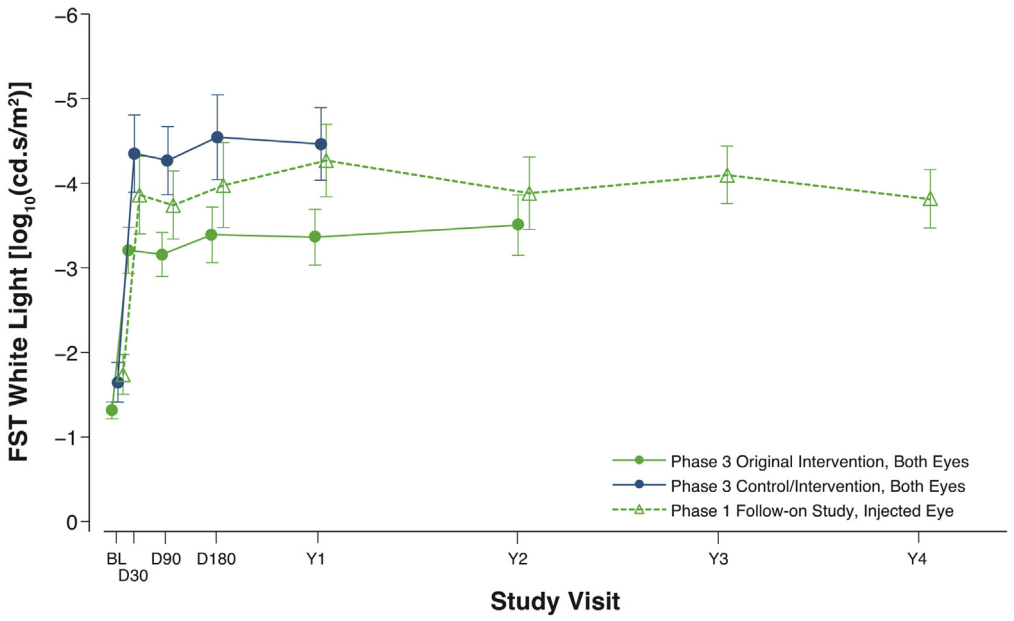

Figure 5. Mean full-field light sensitivity threshold (FST), white light, averaged over both eyes, from administration baseline in evaluable phase 1 follow-on subjects (n = 8) and phase 3 subjects (mITT population). Intervals are ±1 standard error. BL = baseline; cd.s = candela second; D = day; mITT = modified intent-to-treat; Y = year.

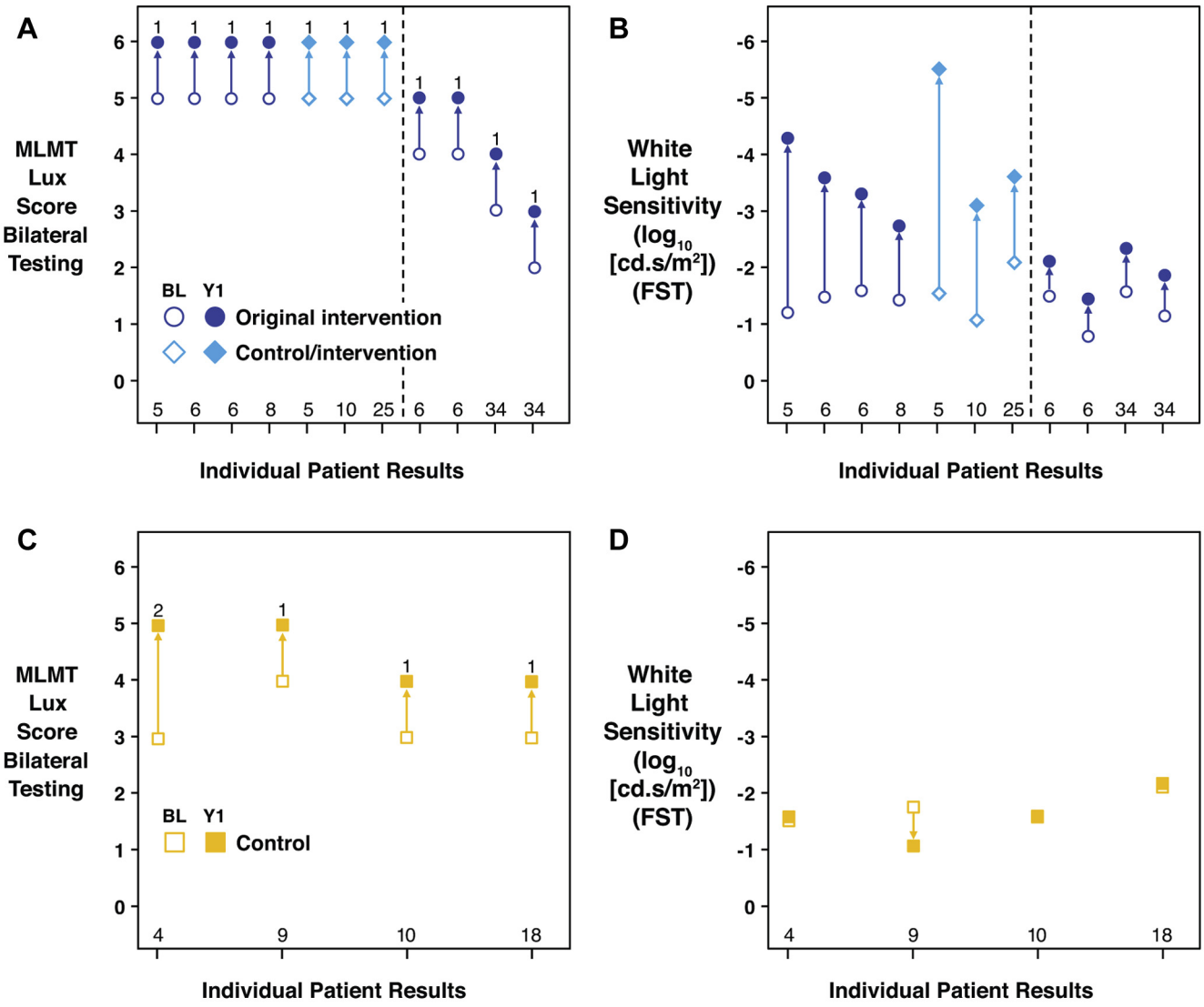

Figure 6. Phase 3 bilateral Multi-Luminance Mobility Test (MLMT) and full-field light sensitivity threshold testing (FST), white light, averaged over both eyes for subjects with MLMT score change of 1 at baseline and year 1. **A,** Treated phase 3 subjects with bilateral MLMT change score of 1 at 1 year after treatment (11 subjects). The first 7 subjects were able to pass at 4 lux at study baseline and thus had a ceiling effect for MLMT improvement. Subject age at first voretigene neparvovec-rzyl (VN) administration is displayed along the x-axis. **B,** The FST for the same 11 subjects. Subject age at first VN administration is displayed along the x-axis. **C,** Control subjects with bilateral MLMT change score of ≥1 during the control year. Subject age at randomization is displayed along the x-axis. **D,** The FST for the same control subjects during the control year. Subject age at randomization is displayed along the x-axis. BL = baseline; Y1 = year 1.

that remained stable at year 2: 312 (295), a 99% increase from baseline. The CI group gained 194 (245) sum total degrees, a 49% increase, at year 1, compared with a 16% loss of −77 (259) sum total degrees over the previous 1-year control period. Test–retest variability in Goldmann kinetic VF area is reported as less than 20% in patients with various forms of retinitis pigmentosa.[19] Although the phase 3 study used the sum total for all 24 meridian degrees rather than total area, the same 20% change value may be appropriate for this assessment. Mean gain exceeded this 20% threshold and has been durable up to 2 years to date.

Safety

Safety data from all subjects who received VN in the phase 1 follow-on and phase 3 studies, whether evaluable on MLMT or not, demonstrate that the intervention has a safety profile consistent with vitrectomy and the subretinal injection procedure. Twenty-seven subjects (68%) had ocular TEAEs, most of which were related primarily to the administration procedure and most of which resolved with minimal or no intervention and without sequelae. Two serious ocular AEs occurred: 1 event of retinal disorder (loss of foveal function) assessed as related to the administration procedure and 1 event of increased intraocular pressure (with associated optic atrophy) in a subject with endophthalmitis who received anti-infectives and a periocular steroid injection. The most common ocular TEAE was cataract, reported in 7 subjects (18%); this was not unexpected given cataract formation is a well-known possible secondary event after a vitrectomy, regardless of the reason for vitrectomy.[20-24] The proportion of subjects with ocular TEAEs across studies

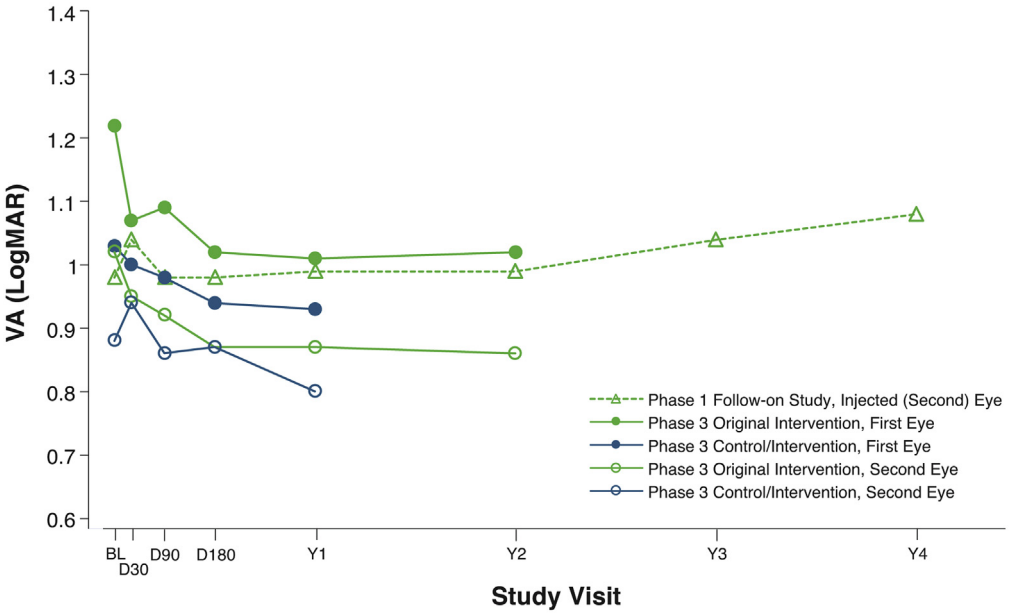

Figure 7. Mean visual acuity (VA) for each eye from administration baseline, by treatment group and study visit using Lange for off-chart acuities in evaluable phase 1 follow-on subjects (n = 8) and phase 3 subjects (mITT population). BL = baseline; logMAR = logarithm of the minimum angle of resolution; mITT = modified intent-to-treat.

is shown in Table 2. Six subjects reported serious TEAEs across the phase 1 follow-on and phase 3 studies; no death or discontinuation due to TEAEs occurred in any of the clinical studies.

Discussion

Over 4 years after administration, subretinal VN gene therapy continues to show a safety profile consistent with vitrectomy and the subretinal injection procedure, as well as stable, persistent improvement in tests of functional vision and visual function in subjects with *RPE65* mutation–associated IRD. Results in phase 1 follow-on subjects—participants who received, in their second eye, the same dose of VN administered in the phase 3 trial using the same surgical procedures and who would have met phase 3 eligibility criteria—are consistent with the results in the phase 3 OI group and those in the phase 3 CI group. The similarity of results across these studies reinforces the developing longer-term efficacy and safety profile of this gene augmentation therapy.

The similarities of the onset and durability of the MLMT treatment responses across both studies and multiple subject populations are apparent in Figure 4. More specifically, maximal, or near maximal, effects were observed by day 30 for each study; moreover, the respective treatment effects were maintained across the evaluated time periods, with a durable change from baseline observed from 1 to 4 years post-vector administration. The MLMT evaluates functional vision by documenting the subject's ability to navigate a mobility course under a variety of specified light levels ranging from 1 lux (equivalent to a moonless summer night) to 400 lux (equivalent to an office environment).[15] The MLMT results approximate the improved ability, in terms of both time and accuracy to perform navigational activities independently during activities of daily living.[15]

Likewise, the similarities of the onset and durability of the FST treatment responses across phase 1 follow-on and phase 3 studies are shown in Figure 5. As with the MLMT, by day 30 in each study, maximal, or near maximal effects, demonstrating more than a 2 $\log_{10}$ units improvement in light sensitivity over the entire VF, were observed. These treatment effects were maintained across the evaluated time periods, again with a durable change from baseline observed from 1 to 4 years post-vector administration. The mean change from administration baseline in all groups (phase 1 follow-on and phase 3 OI and CI) greatly exceeds the reported test–retest variability of ± 0.3 $\log_{10}$ units and a suggested clinical significance threshold of 1 $\log_{10}$ units change.[25]

Full-field light sensitivity threshold testing is a global measure of retinal sensitivity to light. Given that *RPE65* mutation–associated IRD commonly presents with diminished low light sensitivity, FST serves as a relevant visual function test to measure improvement in photoreceptor function. Furthermore, low light sensitivity, or nyctalopia, results in decreased ability to perform tasks, including independent navigation, in moderate or low light conditions. The connection between light sensitivity and navigation under low light conditions is demonstrated by the strong relationship found between the postintervention ability to pass the MLMT at the lowest illuminance level tested (1 lux) and an improvement of FST of >1 $\log_{10}$ units. Furthermore, subjects treated with VN who had a 1 light level improvement in MLMT had corresponding robust improvements in FST, in contrast to control subjects with an

Table 2. Ocular Treatment-Emergent Adverse Event by System Organ Class and Preferred Term: Phase 1 Follow-on Study and Phase 3 Study: All Adverse Events, Data Cutoff May 18, 2016

No. (%) of Subjects MedDRA SOC/PT	Phase 1 Follow-on Study (n = 11)	Phase 3			Total
		Original Intervention (*n* = 20)	*Control/Intervention* (*n* = 9)	*Total* (*n* = 29)	*Phase 1 Follow-on and Phase 3* (*N* = 40)
Any ocular TEAE	8 (73)	12 (60)	7 (78)	19 (66)	27 (68)
Eye disorders	8 (73)	10 (50)	6 (67)	16 (55)	24 (60)
Cataract	3 (27)	4 (20)	0	4 (14)	7 (18)
Chalazion	1 (9)	0	0	0	1 (3)
Choroidal hemorrhage	0	0	1 (11)	1 (3)	1 (3)
Conjunctival cyst	0	1 (5)	0	1 (3)	1 (3)
Conjunctival hyperemia*	0	0	1 (11)	1 (3)	1 (3)
Dellen	3 (27)	0	0	0	3 (8)
Diplopia	1 (9)	0	0	0	1 (3)
Eye inflammation†	1 (9)	2 (10)	0	2 (7)	3 (8)
Eye irritation	1 (9)	1 (5)	0	1 (3)	2 (5)
Eye pain	1 (9)	1 (5)	1 (11)	2 (7)	3 (8)
Eye pruritus	0	1 (5)	1 (11)	2 (7)	2 (5)
Eye swelling	0	1 (5)	0	1 (3)	1 (3)
Foreign body sensation in eyes	0	1 (5)	0	1 (3)	1 (3)
Iritis	0	1 (5)	0	1 (3)	1 (3)
Macular degeneration‡	0	1 (5)	0	1 (3)	1 (3)
Macular hole	0	1 (5)	1 (11)	2 (7)	2 (5)
Maculopathy§	1 (9)	1 (5)	0	1 (3)	2 (5)
Ocular discomfort	0	0	1 (11)	1 (3)	1 (3)
Optic atrophy	1 (9)	0	0	0	1 (3)
Photophobia	1 (9)	0	0	0	1 (3)
Pseudopapilledema	0	1 (5)	0	1 (3)	1 (3)
Retinal deposits‖	0	0	3 (33)	3 (10)	3 (8)
Retinal disorder¶	0	0	1 (11)	1 (3)	1 (3)
Retinal hemorrhage	0	1 (5)	0	1 (3)	1 (3)
Retinal tear#	0	2 (10)	1 (11)	3 (10)	3 (8)
Infections and infestations	0	1 (5)	0	1 (3)	1 (3)
Conjunctivitis viral	0	1 (5)	0	1 (3)	1 (3)
Injury, poisoning, and procedural complications	0	0	1 (11)	1 (3)	1 (3)
Wound dehiscence	0	0	1 (11)	1 (3)	1 (3)
Investigations	2 (18)	4 (20)	1 (11)	5 (17)	7 (18)
Intraocular pressure increased	2 (18)	4 (20)	1 (11)	5 (17)	7 (18)

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
*Includes verbatim terms of suture irritation and suture reaction.
†Including 1 case of endophthalmitis (verbatim term: intraocular inflammation endophthalmitis).
‡Verbatim term: macular thinning.
§Includes verbatim terms of epiretinal membrane and macular pucker.
‖Verbatim term: subretinal precipitate.
¶Includes verbatim terms of foveal thinning and loss of foveal function.
#Intraoperative retinal tears related to sclerotomy incision and treated in standard fashion with laserpexy; no sequelae/no impact on the treatment.

improvement of 1 level in MLMT but no improvement in FST. These results demonstrate the biological effect of VN on retinal function and, more specifically, rod function. However, the ceiling effect inherent in the MLMT can partially limit assessment of improvement in functional vision. Pairing the MLMT with the FST extends the dynamic range of the test for those who exhibit a ceiling effect on MLMT (Fig 6A and B) and corrects for any spurious improvements due to maturation or a learning effect on the MLMT in those who did not undergo any intervention (Fig 6C and D). Whereas the MLMT is a novel end point that may be unfamiliar and unavailable to most clinicians, its relationship with FST provides a clinically feasible means to follow the effects of therapeutic intervention in patients with *RPE65* mutation–associated IRD.

Both Holladay- and Lange-assigned off-chart BCVA values were determined for any assessments of off-chart BCVA in these trials, making comparison among groups straightforward with either method. The use of Lange off-chart assignment may avoid overestimating the effect on BCVA and therefore was used. In addition, monocular BCVA, which reflects clinical practice, was reported and used for calculations across all groups, in addition to the use of BCVA averaged over both eyes in the 1-year phase 3 statistical analysis plan. For these reasons, and to allow accurate comparison among groups, monocular BCVA measurements were used exclusively.

Improvement in BCVA, a measure of foveal, cone-mediated function, was unexpected after VN administration in this predominantly rod-mediated disease. Nonetheless, BCVA showed some evidence of improvement in phase 3 subjects and some stabilization in phase 1 follow-on subjects. These results vary from the general pattern of BCVA loss observed in the natural history of patients with *RPE65* mutation–associated IRD.[18]

In contrast to the average yearly VF loss of approximately 25 sum total degrees on Goldmann VF III4e in the natural history of patients with *RPE65* mutation–associated IRD,[18] phase 3 subjects had a mean (SD) change of +267 (276) sum total degrees at 1 year posttreatment, and OI subjects maintained this increase at 2 years. The increase in sum total degrees indicates an enlarged area of retinal sensitivity, due to increased photoreceptor function, which could translate into increased light sensitivity and improved peripheral vision. Moreover, as shown earlier in a study characterizing the relationship of performance on the MLMT with other tests of visual function,[15] the improvement in Goldmann VF III4e occurred across a boundary (>500 sum total degrees) associated with improved performance on the MLMT. Ongoing observation will assess the durability of these gains in phase 3 subjects.

The efficacy end points measured in the clinical program of VN were developed in dialogue with the Food and Drug Administration; end points that captured a functional change in vision rather than structure/anatomic change were deemed most relevant to the clinical evaluation of VN. The viability of retinal cells as determined by retinal thickness on SD OCT, fundus photography, and clinical examination were essential inclusion criteria for both the phase 1 and phase 3 studies but were not followed in a comparative manner to draw meaningful conclusions. A few electroretinograms (ERGs) were completed in phase 1 and showed a lack of change, but because of the difficultly in performing the test in pediatric subjects and the discomfort to the patient, ERGs were not performed in phase 3. Pupillometry as a proxy for ERGs was used for a period and showed good evidence of effect when a single eye was injected but was more difficult to interpret without an uninjected control eye. Neither OCT nor ERG nor pupillometry met the criterion of measuring functional vision rather than visual function.

Regarding safety, results in the clinical program demonstrate a safety profile consistent with vitrectomy and the subretinal injection procedure. All surgeons were identified as "qualified" because of laboratory experience in delivering subretinal injections and were required to undergo a training program for trial participation. Two serious ocular TEAEs occurred: 1 event of elevated intraocular pressure (with resultant optic atrophy) secondary to treatment for endophthalmitis and 1 event of loss of foveal function. Many ocular events were known complications of intraocular surgery, and most occurred during the first year of follow-up without sequelae. Most ocular events resolved with minimal or no intervention. Early concerns that humoral or cell-mediated responses against AAV2 protein, RPE65 protein, or retinal cells generated after initial exposure to VN would result in substantial toxicity have been reduced, at least for the administration intervals (7–14 days or 1.7–4.6 years) studied. No deleterious immune responses have been observed.

Study Limitations

This first report of the entire cohort of 40 phase 1 follow-on and phase 3 subjects who received 1.5×10^{11} vg of VN in at least 1 eye in these studies demonstrates similar efficacy and safety across subject groups. A study of this size, although small, is notable in a rare disease such as *RPE65* mutation–associated IRD. This study does not provide data on subjects aged less than 4 years or subjects whose baseline visual function or functional vision were better than the inclusion criteria of these trials. Furthermore, ethical concerns led these to be open-label trials, potentially introducing biases, although graders for the MLMT, the primary phase 3 end point, were masked to treatment group. Limitations unique to this report include the difference in mean age between the phase 1 follow-on and phase 3 subjects, although this did not appear to affect MLMT or FST. Minor differences in data collection and analysis between studies, including the number of light levels on the MLMT and monocular VA versus VA averaged over both eyes, were easily reconciled. Finally, the MLMT remains a novel end point that is less familiar than more traditional ophthalmic measures despite its construct and content validity. For this reason, the high correlation between MLMT and FST is clinically useful, because the latter test is available and familiar and can be used to assess response to treatment with VN.

The data presented add to the developing longer-term safety, efficacy, and durability profile of VN gene therapy. After subretinal injection, similar improvements in navigational ability and light sensitivity, and a similar safety profile consistent with the administration procedure were demonstrated among 3 groups (phase 1 follow-on, phase 3 intervention, and phase 3 CI) of subjects with *RPE65* mutation–associated IRD, a population who, until the recent Food and Drug Administration approval of VN, had no approved pharmacologic treatment option. These data suggest that this effect, which is nearly maximal 30 days after administration of VN, is durable for at least 4 years. Ongoing observation will yield additional information about the continued durability of treatment effect and the long-term safety profile. These results underscore the need for accurate diagnosis by genetic testing of patients with IRD who may benefit from this and other potential future gene therapies.

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HUMAN SUBJECTS: Human subjects were included in this study. Each of the reported trials received Institutional Review Board/Ethics Committee approval, which adhered to the tenets of the Declaration of Helsinki. All subjects or their parents/legal guardians gave informed consent, and all related work was Health Insurance Portability and Accountability Act compliant.

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Obtained funding: Maguire, Russell, Wellman, Simonelli, High, Bennett

Overall responsibility: Maguire, Russell, Wellman, Chung, Yu, Tillman, Wittes, Pappas, Simonelli, Leroy, Wright, High, Bennett

Abbreviations and Acronyms:
AE = adverse event; **BCVA** = best-corrected visual acuity; **cd.s** = candela second; **CI** = control/intervention; **ERG** = electroretinogram; **FST** = full-field light sensitivity threshold; **IRD** = inherited retinal dystrophy; **ITT** = intent-to-treat; **logMAR** = logarithm of the minimum angle of resolution; **mITT** = modified intent-to-treat; **MLMT** = Multi-Luminance Mobility Test; **OI** = original intervention; **SD** = standard deviation; **TEAE** = treatment-emergent adverse event; **VA** = visual acuity; **VF** = visual field; **vg** = vector genomes; **VN** = voretigene neparvovec-rzyl.

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