FDA ADVISORY COMMITTEE BRIEFING DOCUMENT

Spark Therapeutics, Inc

LUXTURNA™

(voretigene neparvovec)

MEETING OF THE CELLULAR, TISSUE, AND GENE THERAPIES ADVISORY COMMITTEE

MEETING DATE: October 12, 2017

ADVISORY COMMITTEE BRIEFING MATERIALS:

AVAILABLE FOR PUBLIC RELEASE

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LIST OF ABBREVIATIONS

AAV2	Adeno-Associated Viral Serotype 2
AE	Adverse event
AESI	Adverse event of special interest
ADR	Adverse drug reaction
ANOVA	Analysis of variance
BLA	Biologics License Application
cDNA	Complementary Deoxyribonucleic Acid
CHOP	Children's Hospital of Philadelphia
CLIA	Clinical Laboratory Improvement Amendments
CMV	Cytomegalovirus
CS	Contrast Sensitivity
CβA	Chicken Beta Actin
DSMB	Data and Safety Monitoring Board
EOSRD	Early Onset Severe Retinal Dystrophy
ERG	Electroretinography
FST	Full-Field Light Sensitivity Threshold
ICO	International Council of Ophthalmology
IRD	Inherited Retinal Dystrophy
ITT	Intent to treat (includes all subjects enrolled and randomized)
kb	Kilobase
kDa	Kilodalton
LCA	Leber Congenital Amaurosis
LogMAR	Logarithm of the minimum angle of resolution
LRAT	Lecithin/Retinol Acyltransferase
lux	SI unit of illumination; one lumen per square meter
mITT	Modified intent to treat (includes all subjects exposed to investigational agent)
mL	Milliliter
MLMT	Multi-Luminance Mobility Testing
MTVS	Mobility Testing Validation Study
NOAEL	No Observed Adverse Effect Level
OCT	Optical Coherence Tomography
PLR	Pupillary Light Reflex

PP	Per protocol
PPV	Pars plana vitrectomy
PT	Preferred term
qPCR	Quantitative Polymerase Chain Reaction
RP	Retinitis Pigmentosa
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SECORD	Severe Early Childhood Onset Retinal Dystrophy
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
VA	Visual Acuity
VF	Visual field
vg	Vector Genomes

1 EXECUTIVE SUMMARY

Voretigene neparvovec is a gene therapy vector proposed for the treatment of patients with vision loss due to confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Voretigene neparvovec is administered by subretinal injection to each eye separately (12 ± 6 days apart) in patients with sufficient viable retinal cells as determined by non-invasive means, such as OCT (defined as an area of retina within the posterior pole of > 100 microns thickness) or ophthalmoscopy.

In the normal visual cycle, light activates photoreceptors, where 11-*cis*-retinal is converted to all-*trans* retinal. All-*trans*-retinal is then converted to all-*trans*-retinol, which is transported back to the retinal pigment epithelium (RPE) cells, where 11-*cis*-retinol is regenerated through the action of the all-*trans*-retinyl isomerase, RPE65. Finally, 11-*cis*-retinol is oxidized to 11-*cis*-retinal, completing the visual cycle. In the presence of biallelic mutations in *RPE65*, there is a lack of RPE65 protein and the visual cycle is broken, resulting in progressive vision loss, and ultimately almost all patients progress to near total blindness.

However, despite compromised vision, the retinal anatomy is preserved for a comparatively long period; therefore, supplying the missing enzyme can result in restoration of the visual cycle and improvement in vision. For patients with *RPE65* mutation-associated retinal dystrophy, voretigene neparvovec supplies a functional copy of the *RPE65* gene within the retinal pigment epithelium cells, allowing for restoration of the visual cycle.

There are no FDA approved pharmacological treatments for *RPE65* mutation-associated retinal dystrophy. The FDA has granted Orphan Drug, Breakthrough Therapy, and Rare Pediatric Disease designations for voretigene neparvovec. The clinical development program has shown that voretigene neparvovec improves both functional vision and visual function in patients with *RPE65* mutation-associated retinal dystrophy for up to 3 years, with observation ongoing, and with a safety profile consistent with this type of injection procedure.

1.1 Background and Unmet Need

RPE65 mutation-associated retinal dystrophy is an orphan disease, with an estimated 1,000-3,000 patients affected by this disease in the US.

RPE65 mutation-associated retinal dystrophy is one of many different types of inherited retinal dystrophies (IRDs). These IRDs are clinically heterogeneous and vary widely in their pathogenesis, progression, and mutation inheritance. Decades of research have uncovered that visual impairment can result from mutations in more than 250 different genes. For *RPE65* alone, approximately 125 discrete gene mutations have been identified to date. Prior to both the identification of the specific gene(s) associated with the disease and to genetic testing, precise diagnosis was challenging.

Many different clinical diagnoses have been associated with IRDs based on time of onset, severity, and presenting phenotype. However, distinctions in clinical diagnoses are poorly defined, and may have overlapping features, leading to inaccurate or inconsistent diagnoses. For patients with *RPE65* mutation-associated retinal dystrophy, common clinical diagnoses include Leber congenital amaurosis (LCA), retinitis pigmentosa (RP), and severe early childhood onset

retinal dystrophy (SECORD). With the identification of the underlying genetic cause for the pathophysiology and the advent of genetic testing, accurate diagnoses are now possible; however, genetic testing is not yet used universally.

Regardless of the clinical diagnosis, IRDs lead to significant visual impairment. Patients with biallelic *RPE65* mutation-associated retinal dystrophy suffer from severe and progressive retinal and visual deterioration. Patients may be diagnosed in infancy, or may not reach medical attention until school age, but almost all patients eventually progress to near total blindness.

From a pathophysiologic standpoint, RPE65 is expressed in the RPE cells and is a key enzyme involved in the regeneration of 11-*cis*-retinal. The absence of the enzyme leads eventually to the accumulation of toxic precursors and damage to RPE cells. Damage to RPE cells over time, in turn, results in damage to the photoreceptors, which depend on the RPE cells for cellular metabolism (see Section 2.1). The deficiency in the RPE65 protein mainly affects rod photoreceptors that mediate peripheral vision and the ability to detect and see in low luminance light. Accordingly, the hallmark of *RPE65* mutation-associated retinal dystrophy is nyctalopia, or the inability to see or perceive in dim light. Nyctalopia is accompanied by loss of peripheral vision and visual acuity. Cone photoreceptors are secondarily affected since those cells have an alternative visual cycle pathway. In the early stages of the disease, affected individuals typically have such decreased light sensitivity that they are "night blind" and have great difficulty performing visually-dependent activities of daily living, even under normal daytime lighting conditions. Patients are severely limited in basic abilities such as orientation and navigation in dimly lit areas. While constant access to optimal lighting may help some patients with their symptoms at this earlier stage in the disease progression, the natural progression of the disease leads to continued vision loss and ultimately to near total blindness in almost all patients.

Despite improvements in understanding of the disease pathology and in the ability to provide a molecular diagnosis, therapeutic options are still limited. There are currently no available pharmacologic treatments for this debilitating disease. Physicians can only rely upon tools such as visual aids and assistive devices to help patients compensate for diminishing functional vision.

Given the disease pathology, improvement in functional vision is considered an important goal for improving a patient's ability to perform activities of daily living independently. An improved ability to orient and navigate at lower light levels reflects the potential to gain the capability to safely and accurately conduct additional activities of daily living, in a broader range of settings.

A challenge in the clinical development program for voretigene neparvovec was that few validated functional vision endpoints are available for evaluating treatments for *RPE65* mutation-associated retinal dystrophy. Most ophthalmic evaluations measure visual function, or how the *eyes* perform, including visual acuity (VA), visual field (VF), and contrast sensitivity (CS). Functional vision, on the other hand, assesses how a *person* functions or performs in vision-related activities such as reading, mobility, and navigation. Patients with *RPE65* mutation-associated retinal dystrophy experience nyctalopia, decreased VA, and decreased VF, all of which affect functional vision. The existing functional vision tests do not consider light levels and thus may not reflect performance of activities of daily living across a wide range of environmental lighting conditions.

Thus, in addition to a significant unmet need for treatment of *RPE65* mutation-associated retinal dystrophy, there is a need for an endpoint that incorporates the clinically meaningful and relevant aspects of this disease, such as a test that measures functional vision and integrates input from visual acuity, visual fields, and light sensitivity.

1.2 Product Development Overview

Voretigene neparvovec is an adeno-associated viral serotype 2 (AAV2) gene therapy vector with a cytomegalovirus (CMV) enhancer and chicken β-actin (CβA) promoter driving expression of a complementary deoxyribonucleic acid (cDNA) encoding the wild-type human retinal pigment epithelium 65 kilodalton (kDa) protein (hRPE65). The voretigene neparvovec mechanism of action is gene augmentation to express the normal, functional RPE65 protein in affected cells of the retina.

Voretigene neparvovec is manufactured using triple transfection of HEK293 cells. The downstream purification process separates empty AAV capsids from full AAV capsids, and primarily full particles are administered in the final product. The final voretigene neparvovec product is formulated in a physiologic buffer containing a surfactant to help prevent loss of vector on product contact surfaces.

AAV vectors have been used in clinical studies for over two decades and have an excellent safety profile, with few vector-related adverse events (AEs) reported. The AAV vector payload persists as a predominantly non-integrated form, minimizing the risk of insertional mutagenesis events. AAV2 vectors efficiently transduce RPE cells, making AAV2 the ideal choice for this product.

Pre-clinical studies in mouse models of RPE65 deficiency showed production of RPE65 protein and significant improvements in the visual acuity of the eyes treated with voretigene neparvovec. Consistent with the improvements in retinal and visual function, RPE65 protein was found localized to the RPE cells, but not other retinal cell types. Isomerohydrolase activity was demonstrated in lysates prepared from eyecups of affected mice following administered voretigene neparvovec. In a dog model of RPE65 deficiency, administration of voretigene neparvovec resulted in stable recovery of retinal function as evaluated by electroretinography (ERG) and recovery of the visual cycle as demonstrated by detection of 11-*cis*-retinal in the treated areas. Animals treated with voretigene neparvovec showed significantly improved navigation and pupillary light responses, decreased frequency of nystagmus, as well as improved ERGs and visual behavior.

Biodistribution studies in dogs and non-human primates (NHPs) revealed that vector DNA was mainly localized to the intraocular fluids, with weak signals in the optic nerves and optic chiasm. The proposed therapeutic dose of voretigene neparvovec ($1.5x10^{11}$ [1.5E11] vector genomes [vg]/eye) is below the no-observed-adverse-event level (NOAEL) in animals (7.5E11 vg/eye). Safety studies in juvenile mice and dogs showed no vector-related AEs.

In clinical studies, the biodistribution and shedding of voretigene neparvovec vector DNA were determined in whole blood, serum, and tear samples using a quantitative polymerase chain reaction (qPCR) method. Overall, transient and low levels of vector DNA were detected in tear and occasional serum samples.

The non-clinical and PK findings support the safety and efficacy of voretigene neparvovec as a gene therapy for the treatment of *RPE65* mutation-associated retinal dystrophy. The clinical development program for voretigene neparvovec comprised a Natural History Study, a Mobility Testing Validation Study, two Phase 1 studies (Studies 101 and 102), and a Phase 3 pivotal study (Study 301).

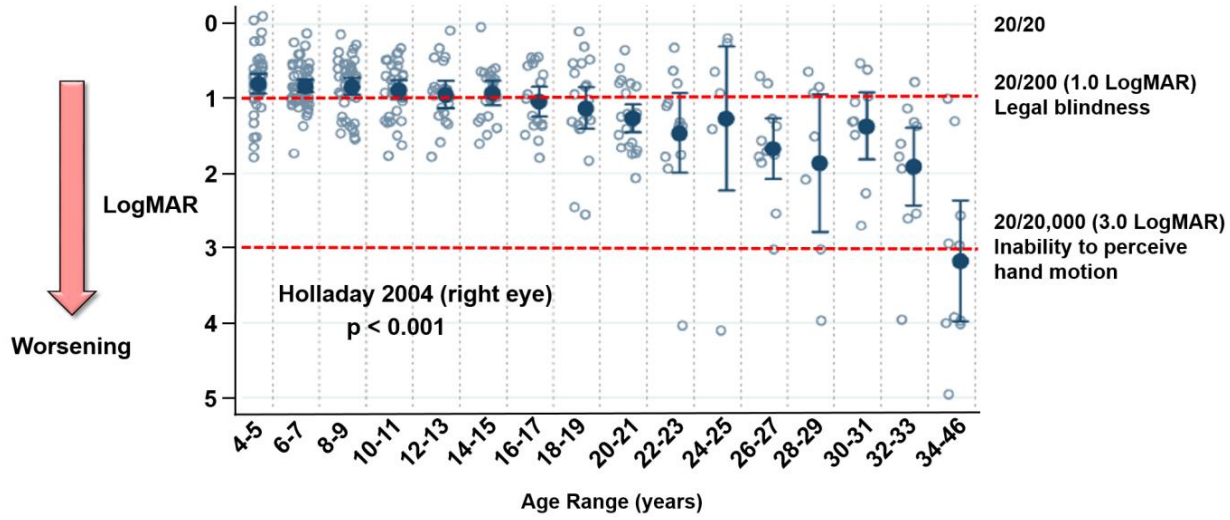
1.3 Natural History Study

There are limited historical data characterizing the natural progression of *RPE65* mutation-associated retinal dystrophy, and much of the data available are confounded by the use of multiple clinical diagnoses that appear to have been inconsistently assigned to similar clinical presentations. To address this, Spark Therapeutics conducted a retrospective chart review (the Natural History Study) of patients with confirmed biallelic *RPE65* mutations to characterize the condition more fully. The Natural History Study included data from the charts of all patients who met eligibility criteria (70 patients) from 7 internationally recognized IRD referral centers. Chart records were reviewed to collect information on ocular history and clinical testing, including VA, VF, and OCT testing data from the time of presentation to the referral center until the last recorded visit in the chart. In addition, electroretinography, and comprehensive ophthalmic examination data were also collected, where available.

The study included charts of patients with *RPE65* mutation-associated IRD confirmed by genetic testing. These patients were males and females born between January 1, 1963 and December 31, 2010 with genetic diagnoses consistent with autosomal recessive mutations, homozygous or compound heterozygous, in the *RPE65* gene. The average age of patients at the first recorded visit to a study site was 15 years, with a range of one to 43 years. The average duration between first and last visits was 7.3 years (median 4.5), ranging up to 33 years for one subject chart. The study population was 60% female, 67% white, and predominantly non-Hispanic or Latino. Fifty-six unique *RPE65* mutations were represented in the cohort.

Overall, the results of the Natural History Study showed an early and profound compromise in visual function in patients with *RPE65* mutation-associated IRD. Visual acuity data was modeled separately for each eye to assess the association with age. The mixed effects polynomial regression model identified statistically significant quadratic trends of age on VA, which were statistically significant ($p<0.0001$) for each eye. It should be noted that age was used as a proxy for progression of disease in the Natural History Study, since this was the only available information. Age may not always reliably indicate the extent of disease with respect to functioning retinal cells. While there was individual variability, VA was worse with increasing age, based on testing performed in the 20-40 year age group (Figure 1). Around the age of 16, the average logarithm of the minimum angle of resolution (LogMAR) begins to exceed 1.0 (equivalent to 20/200), which is the International Council of Ophthalmology's (ICO) threshold for severe visual impairment and the criteria for "legal blindness" in the US. By the age of 18, more than half of the patients in the study were legally blind, as defined by visual acuity of the better eye. This was a notable finding considering that some central vision can be preserved until the third decade of life. Patients in the oldest age grouping in the study (34-46 years) showed worse VA, with a mean LogMAR exceeding 2.0 (equivalent to 20/2000).

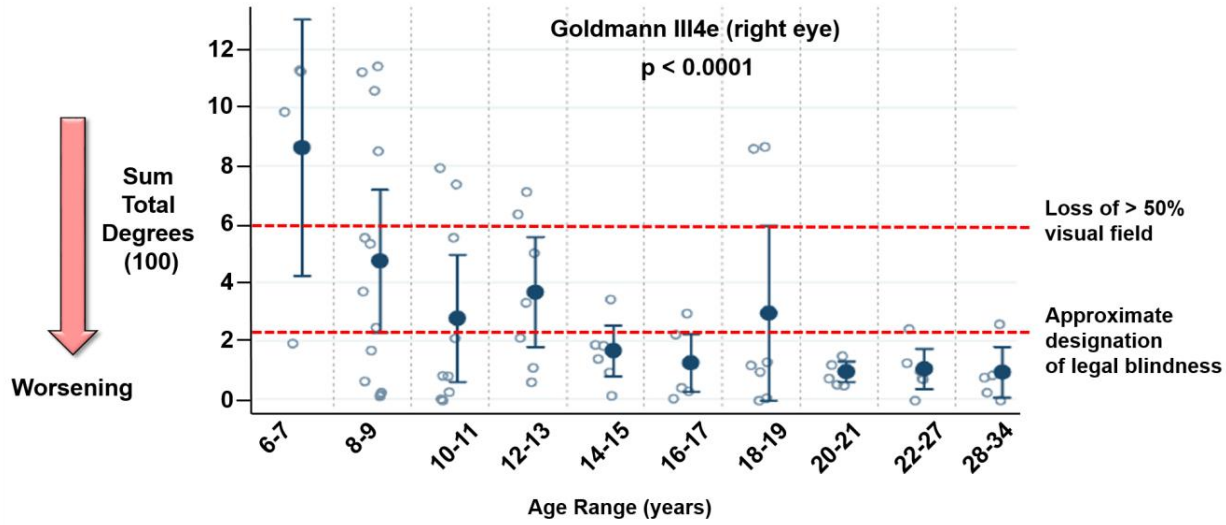
Figure 1: Visual Acuity Results in the Natural History Study



Bars represent mean and 95% confidence interval for each age grouping. Dots represent actual values.

Similar results were observed for VF testing (Figure 2). Goldmann perimetry was used to assess the full extent of the VF for each eye by testing patients' ability to detect differing sizes and intensities of light in their periphery. Two different test stimuli, III4e and V4e, were used for Goldmann VF testing; the smaller III4e test stimulus is used in visual disability determinations and provides a reference for traditional measures of visual impairment (e.g., legal blindness). The repeated III4e and V4e measurements were analyzed using mixed effects linear regression models. In the two separate left and right eye models, the marginal linear effects of age were significant for III4e ($p<0.0001$) and for V4e ($p<0.0001$). Declining VF was associated with advancing age, including during the first and second decades of life. Beginning in the youngest study age group for whom VF results were available, six to seven years, the Natural History Study cohort had approximately two-thirds or less of the total possible VF for individuals with normal vision. In the eight to nine-year age group, VFs were reduced to 50% or less of normal. Around age 14-15 years, the degree of impairment as measured by Goldmann VF III4e was below 235 sum total degrees (representing one-sixth of the normal VF), which is the International Council of Ophthalmology's (ICO) threshold for severe visual impairment and the "legal blindness" visual field criteria in the US.

Figure 2: Visual Field Results in the Natural History Study



Bars represent mean and 95% confidence interval for each age grouping. Dots represent actual values.

Overall, the results of the Natural History Study illustrate the serious and progressive visual function loss due to *RPE65* mutation-associated retinal dystrophy.

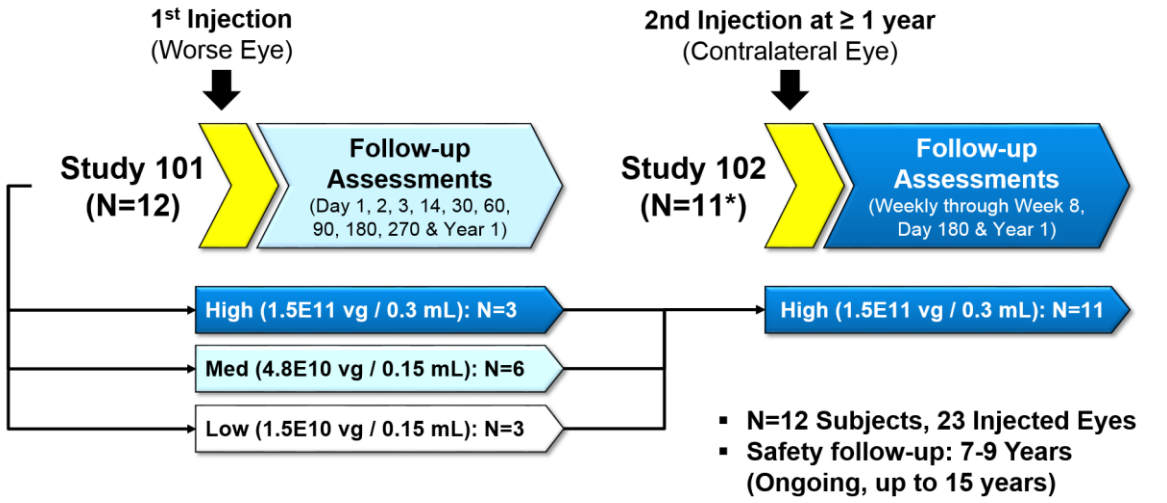
1.4 Efficacy

Substantial evidence of efficacy comes from the pivotal Phase 3 study, Study 301, and is supported by the Phase 1 studies.

1.4.1 Phase 1

The Phase 1 program consisted of two studies, Studies 101 and 102, designed primarily to assess the safety and tolerability of subretinal administration of voretigene neparvovec, and secondarily to evaluate a number of clinical measures of efficacy in human subjects (Figure 3). Study 101 was a dose-escalation study in which the worse of the two eyes of eligible subjects (n=12) was identified and administered one of three doses: 1.5E10, 4.8E10, or 1.5E11 vg. Study 102 was a follow-on study in which eligible subjects from Study 101 (n=11) underwent administration to the contralateral eye of voretigene neparvovec at the dose selected for further study from Study 101 (1.5E11 vg). Injection of the second eye occurred after at least one year of follow-up in the initial study.

Figure 3: Design of Phase 1 Studies



*One subject did not meet eligibility criteria for contralateral eye injection due to glaucoma

For Phase 1, subjects had to be at least eight years of age with *RPE65* mutations confirmed by a Clinical Laboratory Improvement Amendments (CLIA) certified genetic testing laboratory. Visual acuity had to be worse than or equal to 20/160 or subjects had to have a VF of less than 20 degrees in any of the 24 meridians in the eye to be injected. In addition, all subjects had to have sufficient viable retinal cells as determined by non-invasive testing such as ophthalmoscopy or OCT. Because Study 102 was a follow-on study, the enrollment criteria were similar. Only subjects from Study 101 with at least 1 year of follow-up were eligible for Study 102. In addition, subjects had to have VA of at least light perception and sufficient viable retinal cells in the contralateral eye.

At the time of initiation of Phase 1, there was no precedent for testing the effects of therapy in individuals with profoundly low vision due to mutations in *RPE65*. The primary objective of the Phase 1 studies was to determine the safety and tolerability of voretigene neparvovec in the target population; secondary endpoints included a variety of efficacy measures in order to evaluate changes in visual function and functional vision. These endpoints included VA, VF, Full-Field Light Sensitivity Threshold (FST) and mobility testing (detailed in Sections 5 and 6).

Study 102 included an exploratory version of the multi-luminance mobility test (MLMT) as an additional assessment to analyze changes in functional vision. The MLMT was optimized and refined in Phase 1, and a standardized version was subsequently utilized as the primary endpoint in Phase 3 (described in Section 5).

Twelve subjects were enrolled in Study 101 (Table 1). The mean age at first study visit was approximately 21 years and ranged from age 8 to 44. Approximately 60% of the subjects were male, and the majority were white. One subject from Study 101 did not meet eligibility criteria for administration to the contralateral eye due to the presence of glaucoma in the uninjected eye and therefore was not included in Study 102.

Table 1: Demographic Characteristics in Study 101

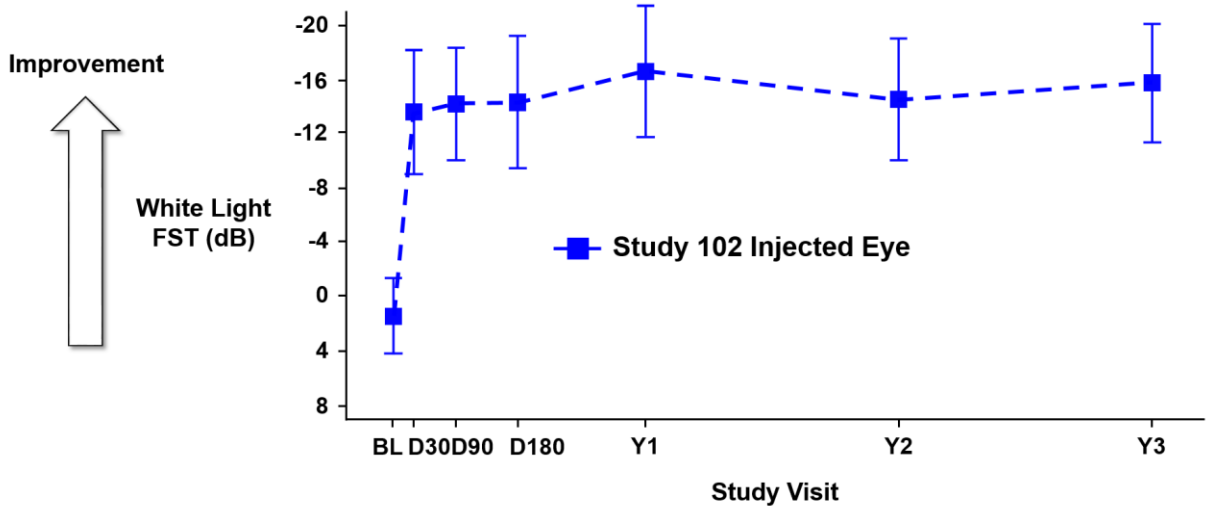
Variable	Study 101 (N=12)
Mean Age (Years)	20.8
Range	8 - 44
Male	58%
White	92%
Non-Hispanic	100%

In Study 101, three subjects received 1.5E10 vg in a volume of 0.15 mL, six subjects received 4.8E10 in a volume of 0.15 mL, and three subjects received 1.5E11 vg in a volume of 0.3 mL. Follow-up assessments were taken at multiple timepoints throughout the first year after administration. All subjects enrolled in any of the Phase 1 or Phase 3 clinical studies for voretigene neparvovec have enrolled in a long-term follow-up study and will be followed for 15 years after administration. Assessments will include mobility testing, FST, VA, and VF, as well as a visual function questionnaire and safety assessments.

Results from Study 101 showed signs of efficacy, but no clear dose response, possibly due to the wide phenotypic variations in the subject population. All three dose cohorts showed a similar safety profile. The high dose of 1.5E11vg in a volume of 0.3 mL was selected, as the increased volume targets a larger portion of the retina and may provide a greater likelihood of direct benefit to the individual subjects. This dose was used for all subjects enrolled in Study 102, as well as those in the Phase 3 study. Increasing the dose even two-fold would require either increasing the volume to 0.6 mL or increasing the concentration of the vector to 1E12 vg/mL, neither of which were considered desirable. Thus, it was determined that increasing the dose would introduce greater potential for risk without clear evidence of benefit, especially because vector-related toxicity would likely be irreversible.

Full-field light sensitivity threshold testing results from Study 102 indicate that the majority of subjects were able to respond at a lower light intensity following voretigene neparvovec administration (Figure 4). Note that the x-axis begins at baseline (BL) for the second eye (Study 102 eye), at which point the first eye has already been injected at least one-year prior, at a range of doses. Given the mechanism of action for voretigene neparvovec, the functional improvement at lower light levels is clinically relevant to patients suffering from this disease, as its progression often leads to decreased light sensitivity and night blindness.

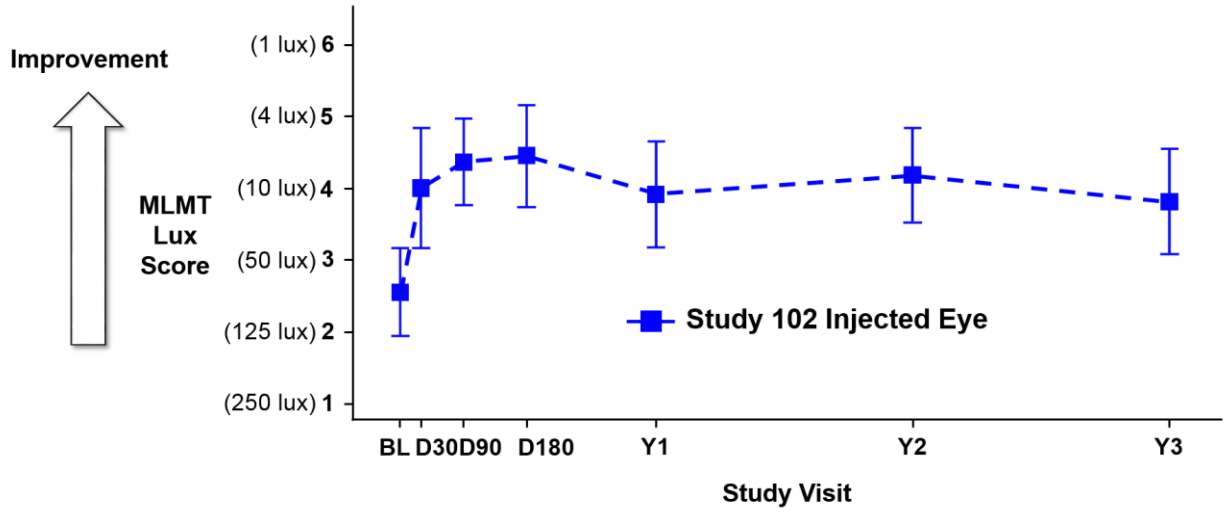
Figure 4: Full-Field Light Sensitivity Threshold Testing in Study 102



BL: Baseline; N = 11. Data presented as mean ± SE

During the course of Study 102, the mobility test was refined and standardized. (Figure 5). Five of the 11 subjects (45%) received the maximum attainable score, indicating that they could successfully navigate the course at the lowest light level tested. Following vector injection, there was a rapid and sustained improvement in the mobility test score change for the Study 102 eye.

Figure 5: Mobility Testing Results in Study 102



BL: Baseline; N = 11. Data presented as mean ± SE

Overall, the durability of response across all evaluations in the Phase 1 studies supports the long-term benefit of voretigene neparvovec therapy. In the second injected eyes, VA slightly improved in the majority of subjects, and all subjects showed improvements in FST and mobility testing. In the first injected, worse eyes, the majority of subjects demonstrated improvements in

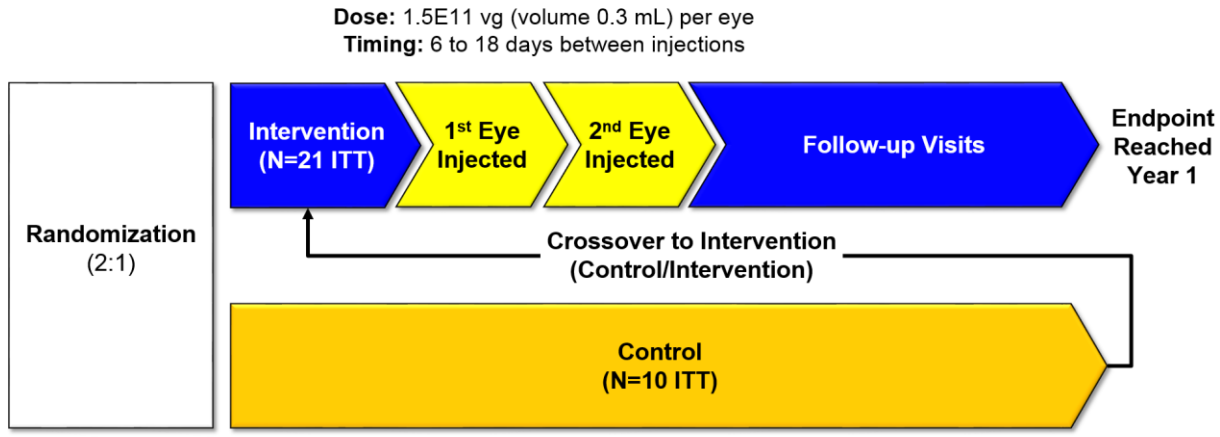
visual function, including visual acuity, at one year. The Phase 1 studies established the safety of injection at the dose selected, and were informative with respect to selecting relevant, clinically meaningful endpoints that take into account the mechanism of action of voretigene neparvovec as well as the clinical deficits associated with *RPE65* mutation-associated retinal dystrophy.

1.4.2 Phase 3

1.4.2.1 Study Design

Study 301 was an open-label randomized controlled Phase 3 study in which subjects with confirmed biallelic *RPE65* mutations were randomized in a 2:1 fashion to either the voretigene neparvovec group (1.5E11 vg; referred to as the Intervention group) or Control group and followed for one year (Figure 6). After completion of one year of observation, Control subjects were allowed to crossover and receive voretigene neparvovec treatment (referred to as the Control/Intervention group after crossover). Additionally, all subjects in the clinical program have been enrolled in a long-term follow-up study and will be followed for 15 years after vector administration.

Figure 6: Phase 3 Study Design



mITT (N=29): 1 Control subject withdrew consent; personal reasons. 1 Intervention subject withdrawn by physician; medical concerns.

Based on the safety data generated in Phase 1, the Phase 3 study was allowed to enroll children as young as three years of age. Subjects randomized to the Intervention group received near-simultaneous (no more than 18 days [12 days ± 6 days] apart), sequential injections of 1.5E11 vg voretigene neparvovec in a volume of 0.3 mL to each eye, while subjects randomized to the Control group completed the same series of observations, but without vector administration, for a period of at least one year from the Baseline evaluation. To evaluate efficacy, the endpoints (change from Baseline) were compared between the Intervention and Control groups at one year for the pivotal portion of this study. After one year of observation, all Control subjects then crossed over and received sequential bilateral injections of voretigene neparvovec (i.e., the Control/Intervention group).

Enrollment criteria for Study 301 included the following:

- Subjects had to be at least three years of age with confirmed biallelic *RPE65* mutations.
- Subjects had to have a VA of worse than or equal to 20/60 (for both eyes) and/or VF less than 20 degrees in any meridian as measured by a GVF III4e isopter or equivalent (both eyes).
- Subjects had to have sufficient viable retinal cells as determined by non-invasive means, such as OCT (defined as an area of retina within the posterior pole of > 100 microns thickness) or ophthalmoscopy.
- Subjects had to have the ability to comprehend the MLMT, follow course instructions, and the capacity to successfully navigate the course.
- Subjects had to have a baseline score on the MLMT that would allow a measurable improvement to be observed (i.e., they could not have a passing score at the lowest light level of 1 lux at study entry). In addition, subjects had to have an accuracy score of ≤ 1 (where a score of 0 means no errors) at 400 lux.

The pre-specified primary efficacy endpoint was the change from Baseline at Year 1 in MLMT performance using the bilateral testing condition of the Intervention group compared to Controls. Recognizing the need for a quantifiable endpoint relevant to the specific symptoms of the disease, Spark Therapeutics developed the MLMT as a novel endpoint to measure functional vision across a range of luminance levels in patients with *RPE65* mutations. The MLMT endpoint used in Phase 3 evolved from exploratory mobility testing in Phase 1 and showed construct and content validity in the Mobility Test Validation Study (MTVS; Chung et al. (2017); see Section 5 for details).

The MLMT is a task that challenges a subject to navigate a course independently and accurately under differing light conditions within a time limit. There are 12 different standardized courses (Figure 7) for the MLMT, each with the same number of turns and obstacles. The test is conducted at seven different light levels, from 1 lux to 400 lux, which span a wide range of environmental lighting conditions commonly encountered during the course of everyday activities (Table 2).

Figure 7: Example of MLMT Course

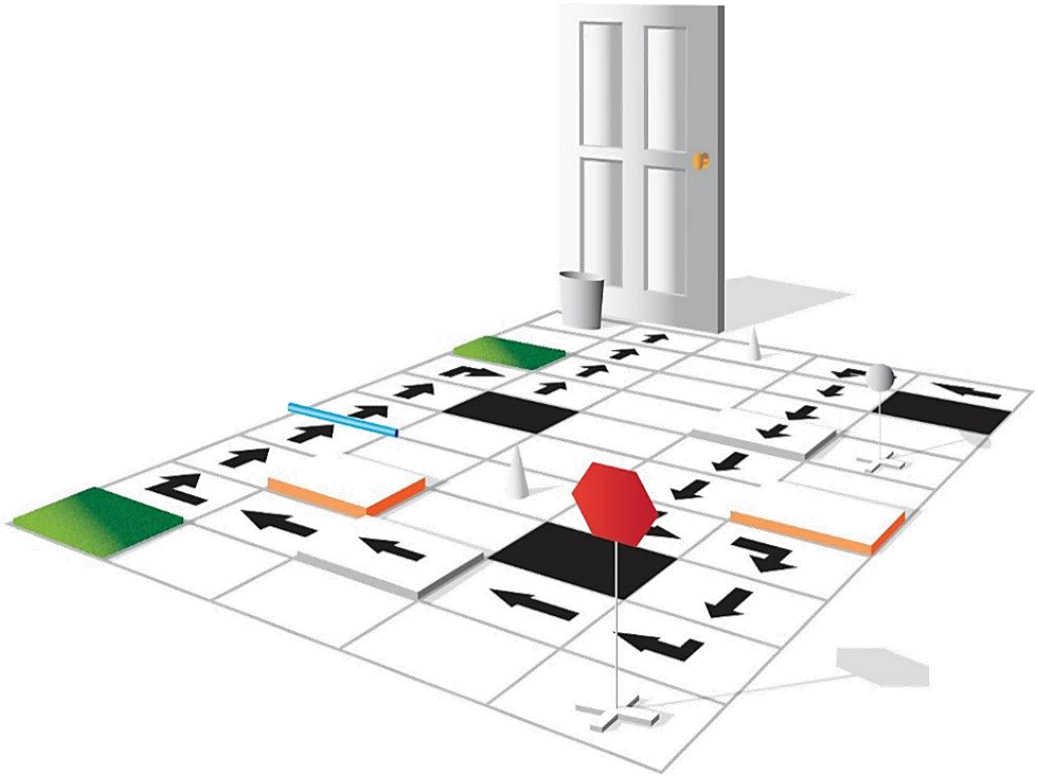
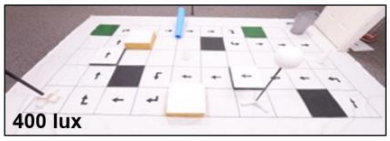


Table 2: Light Levels for Multi-Luminance Mobility Test

Light Levels	Examples
1 lux	Moonless summer night; Indoor nightlight
4 lux	Cloudless night with half moon; Parking lot at night
10 lux	1 hour after sunset in city; Bus stop at night
50 lux	Outdoor train station at night; Inside of lighted stairwell
125 lux	30 minutes before sunrise; Interior of train / bus at night
250 lux	Interior of elevator or office hallway
400 lux	Office environment or food court



Light meter: National Institute of Standards and Technology-calibrated,
Extech model #EA33 light meters used to provide examples and to set / verify specified light levels used for mobility testing

Following 40 minutes of dark adaptation, participants complete the course with one eye patched, then complete a new course configuration with the other eye patched, and then a third

configuration with neither eye patched. Each test run of a subject, at differing light intensities and on randomly selected courses, is videotaped and assessed by two masked, independent graders using a defined combination of speed and accuracy scores. The graders assign each course completion either a "pass" or "fail," depending on whether the subject navigated the course within a fixed time limit (< 180 seconds in Phase 3) and with a minimum number of errors (three in Phase 3) at the light level being tested. This process is repeated for at least two light levels (one failing, one passing), or more if required to identify the failing and passing levels for each eye patching condition, progressing from lower to higher light levels, at each time point in the study. Details of the grading rubric, method of training graders, and statistics on inter- and intra-grader agreement are reviewed in Section 5.

To quantify subjects' performance over time, the MLMT score change was used in Study 301. Each of the seven light levels was assigned a lux score, from 0 to 6 (Table 3). The MLMT score change was determined using the difference in lux score for the lowest light level passed at Baseline to the lux score for the lowest light level passed at Year 1. For example, a subject able to achieve a passing score at 125 lux at Baseline would have a lux score of 2, since 125 lux is the lowest light level at which the subject obtained a passing score. If the subject passes at 1 lux (lux score of 6) at 1 year, the MLMT score change would be 4 light levels. Additional details of scoring are provided in Section 5.

Table 3: MLMT Lux Score

Light Level	MLMT Lux Score
1 lux	6
4 lux	5
10 lux	4
50 lux	3
125 lux	2
250 lux	1
400 lux	0

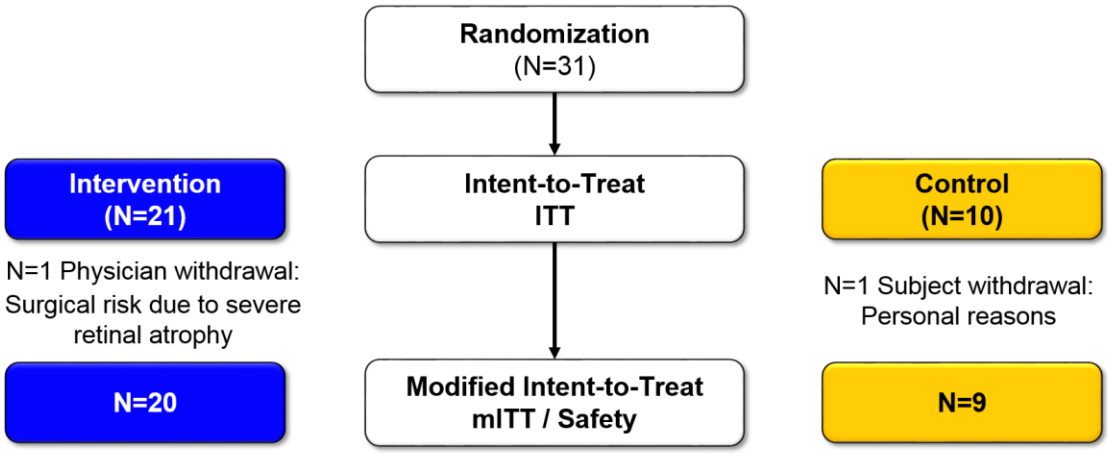
Given the progressive nature of *RPE65* mutation-associated retinal dystrophy, a change of one light level in passing the MLMT was considered clinically significant. As a specific example, 125 lux is equivalent to the interior of a bus or train at night, and 50 lux is the brightness of an indoor stairwell or outdoor train station at night. While an individual might be able to safely navigate the interior of a train car (125 lux) for a commute at night, he/she might have difficulty at an outdoor train station at night (50 lux), which could preclude the use of that method of transportation and limit the mobility of the individual. An improvement of one light level (125 lux to 50 lux) would allow the individual to independently use the train for his or her commute. This change represents a positive impact on an activity of daily living and a clinically meaningful improvement.

Three secondary endpoints, treatment difference of Year 1 changes, were also evaluated, in hierarchical order: FST white light averaged over both eyes, monocular MLMT score change (for the first eye), and VA averaged over both eyes. Visual fields were also examined as an additional exploratory endpoint using both Goldmann kinetic perimetry and Humphrey static microperimetry. See Section 6.5 for a discussion of endpoint selection in Phase 3.

1.4.2.2 Results

A total of 31 subjects were randomized, 21 to the Intervention arm and 10 to Control (Figure 8). Two subjects (one in each group) withdrew or were withdrawn after randomization, prior to receiving any intervention, and prior to any of the following people knowing the treatment assignment: the subject, parent, Principal Investigator, or Medical Monitor. One Intervention subject was withdrawn by the physician due to concerns regarding surgical risk in the setting of severe retinal thinning, and one Control subject withdrew consent due to personal reasons. Therefore, the modified intent to treat (mITT) and Safety Populations comprised 20 Intervention and nine Control subjects. All 29 of these subjects received bilateral injections of voretigene neparvovec.

Figure 8: Subject Disposition in Study 301



The mean age at randomization was approximately 15 years with subjects ranging from four to 44 years of age (Table 4). Approximately 40% of subjects were male, and the majority were white. Most subjects were from the US, and there were also subjects from Europe, other countries in North America, and India. The enrolled subjects reflected a wide range of clinical presentation, reporting mild to severe impairment of visual function and functional vision at baseline. As expected with *RPE65* mutations, all subjects had history of nystagmus and retinal abnormalities, and a few had cataracts or lens opacities at baseline.

Table 4: Subject Demographic Characteristics in Study 301 (ITT population)

	Intervention (N=21)	Control (N=10)
Mean (SD) Age at Randomization (Range)	14.7 (11.8) (4 – 44)	15.9 (9.5) (4 – 31)
Male	9 (43%)	4 (40%)
Race		
White	14 (67%)	7 (70%)
Asian	3 (14%)	2 (20%)
American Indian or Alaska Native	2 (10%)	1 (10%)
Black or African American	2 (10%)	0
Ethnicity (Not Hispanic)	16 (76%)	9 (90%)
US Resident	17 (81%)	6 (60%)

A summary of the findings from the primary and key secondary endpoints is shown in Table 5.

Table 5: Summary of Efficacy Findings, Year 1 Compared to Baseline, from Study 301 (ITT)

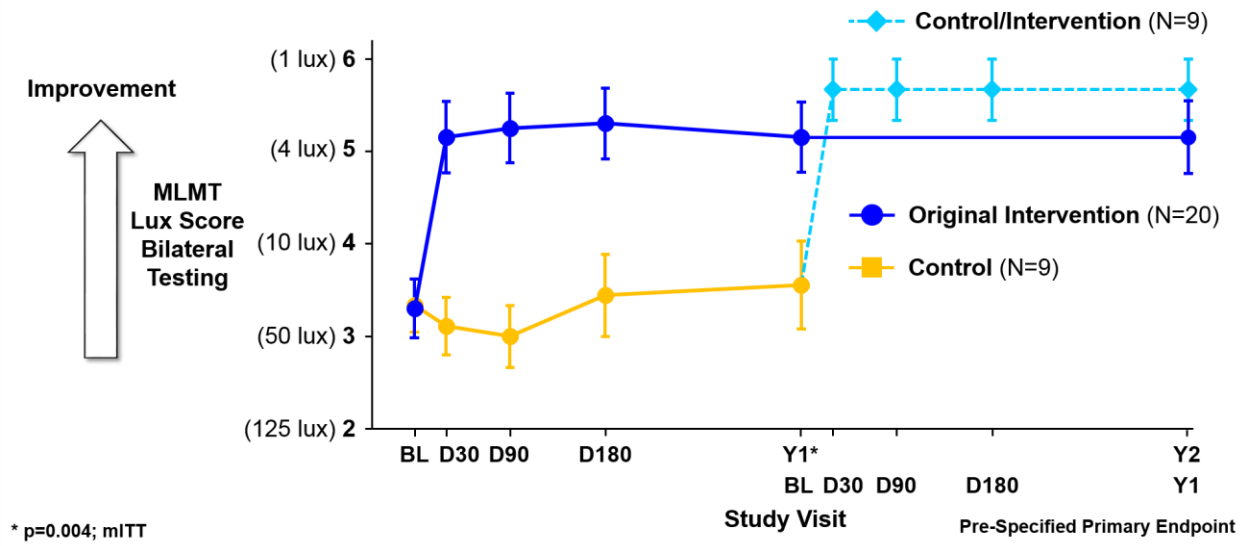
Assessment	**Measurement**	**Mean Difference (95% CI) (Intervention-Control)**	**Statistical Significance (*p*-value)**
Primary Endpoint			
MLMT performance	Bilateral, score change	1.6 (0.72, 2.41)	***p* = 0.001**
Secondary Endpoints			
FST testing	White light averaged over both eyes, log10(cd.s/m^2)	-2.11 (-3.19, -1.04)	***p* < 0.001**
MLMT performance	Assigned first eye, score change	1.7 (0.89, 2.52)	***p* = 0.001**
Visual acuity	Averaged over both eyes, LogMAR (Holladay)	-0.16 (-0.41, 0.08)	***p* = 0.17**
Additional Endpoint			
Visual field	Goldmann III4e sum total degrees, averaged over both eyes	378.7 (145.5, 612.0)	**Nominal *p* = 0.006**
	Humphrey mean macula threshold, dB, averaged over both eyes	7.9 (3.5, 12.2)	**Nominal *p* < 0.001**

Study 301 demonstrated statistically significant results for the primary endpoint; at Year 1, the difference and 95% CI in mean score change between the Intervention (1.8) and Control groups (0.2) was 1.6 (0.72, 2.41) light levels (p=0.001; ITT). A change of one light level in passing the MLMT was considered clinically significant (see Section 5.2 for details). The observed mean MLMT bilateral lux scores are presented over time in Figure 9 for the mITT population. Improvements in the Intervention group were apparent as early as Day 30 and were sustained over the one year of observation, while the Controls showed no change before crossing over.

At Year 1, all nine Control subjects crossed over and received bilateral injections of voretigene neparvovec. This Control/Intervention group also experienced substantial improvements in functional vision, as measured by the mean bilateral MLMT score change at 30 days post-administration. Similar to the Original Intervention group, these benefits were maintained through the first year after administration.

Overall, 72% of all treated subjects (21 of 29) achieved the maximum possible MLMT improvement one-year post-administration, demonstrating significant improvement in functional vision at lower light levels. The benefits observed at one year in the Original Intervention group continued through at least two years post-administration, with observation ongoing.

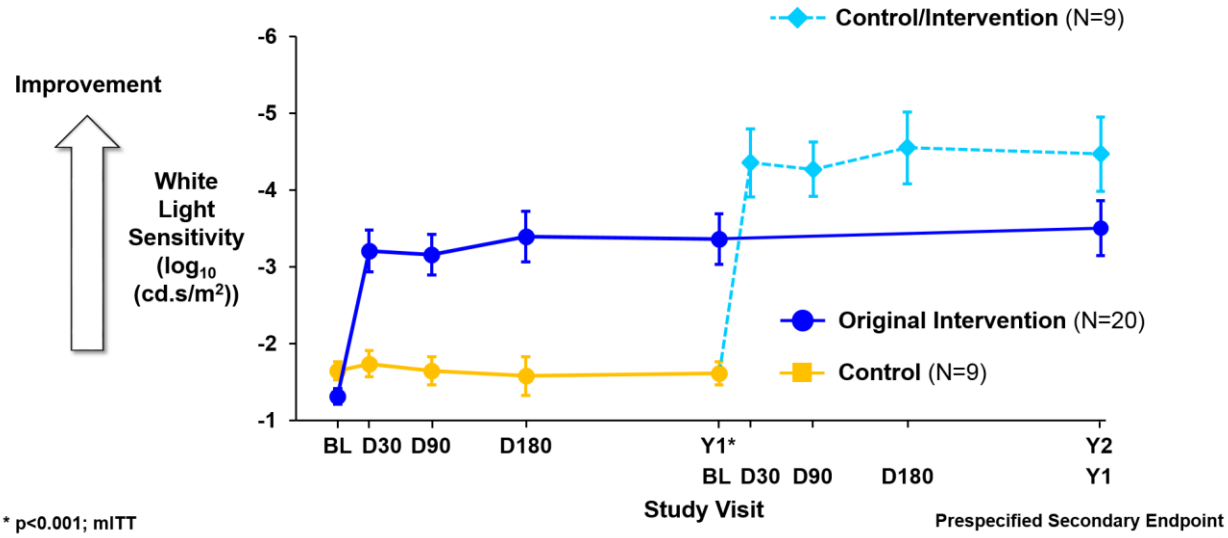
Figure 9: Observed Mean Bilateral Lux Score Over Time in Phase 3 (mITT)



As pre-specified in the Statistical Analysis Plan, since the primary efficacy endpoint was statistically significant, the secondary endpoints were formally tested per the hierarchical order: FST, monocular MLMT for the first eye, and VA.

The first secondary endpoint was FST testing with white light, averaged over both eyes. Full-field Light Sensitivity testing assesses light sensitivity of the entire retina by measuring the subject's perception of different luminance levels. At Year 1, the Intervention group showed a statistically significant (p<0.001; ITT) improvement compared to the Control group, with a modeled treatment group difference (95% CI) of -2.11 (-3.19, -1.04) log10(cd.s/m^2). For this unit of measure [log10(cd.s/m2)], a more negative result indicates a lower threshold and thus improved light sensitivity. The observed FST means are presented in Figure 10 for the mITT population. Similar to the primary endpoint, the benefits of voretigene neparvovec were observed at Day 30 and continued throughout the first two years of the study. After crossing over, similar results were observed in the Control/Intervention group.

Figure 10: Observed Mean FST White Light Over Time in Phase 3 (mITT)



The second secondary endpoint, treatment difference in monocular MLMT performance score change at Year 1 for the first eye, was also statistically significant (*p*=0.001; ITT; Table 6), and showed results that were similar to the bilateral MLMT results.

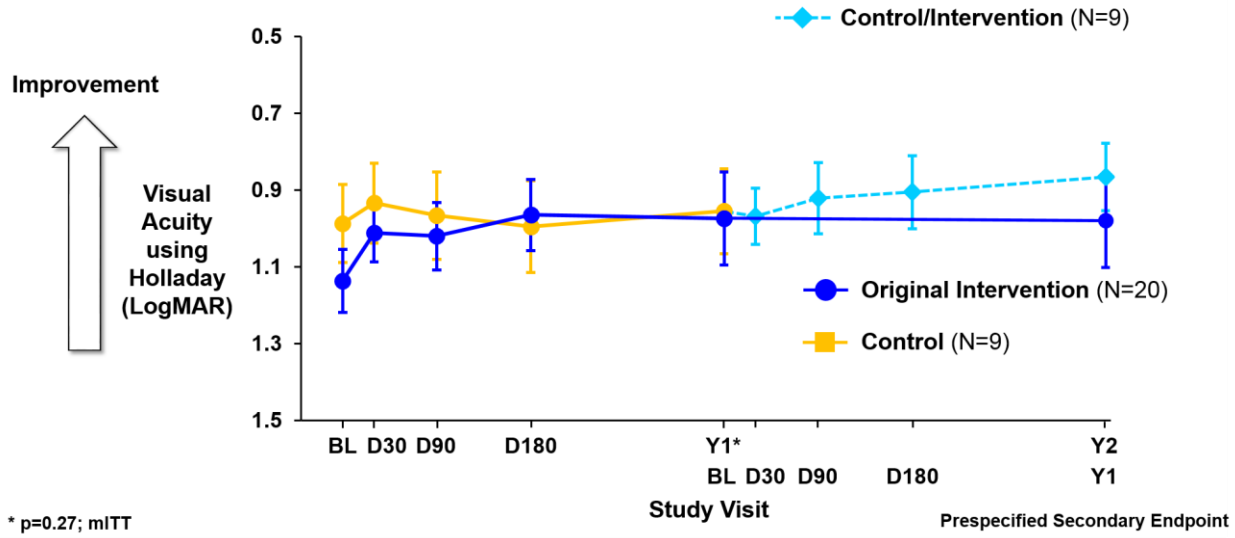
Table 6: MLMT Score Change: First Eye, Year 1 Compared to Baseline in Study 301 (ITT)

First eye	Intervention N=21	Control N=10	Difference (95% CI) (Intervention-Control)	Permutation test *p*-value
Score change				
Mean (SD)	1.9 (1.2)	0.2 (0.6)	1.7 (0.89, 2.52)	0.001
Range (min, max)	0, 4	-1, 1		
Quartiles (25th, median, 75th)	1, 2, 3	0, 0, 1		

The third secondary endpoint, treatment difference of change at Year 1 in VA, averaged over both eyes, was assessed using an adaptation from the scale described by Holladay (2004) for assigning LogMAR to off-chart results. Normal 20/20 vision is equal to a LogMAR of 0, while 20/200 vision is equal to a LogMAR of 1. At Year 1, the modeled treatment group difference (Intervention-Control) (95% CI) was -0.16 (-0.41, 0.08) LogMAR, which was not statistically significant (*p*=0.17; ITT). The observed VA means are presented in Figure 11 for the mITT population. At Year 1, Intervention subjects improved on average by 8.1 letters on an eye chart, and Control subjects by 1.6 letters. After crossing over, the Control/Intervention group improved on average by 4.5 letters.

An additional VA analysis using the Lange et al. (2009) resulted in the same treatment effect but reduced variability, with a treatment difference and 95% CI of -0.16 (-0.41, 0.08, ITT). The nominal *p*-value was 0.035.

Figure 11: Observed Mean Visual Acuity Testing Over Time in Phase 3 (mITT)

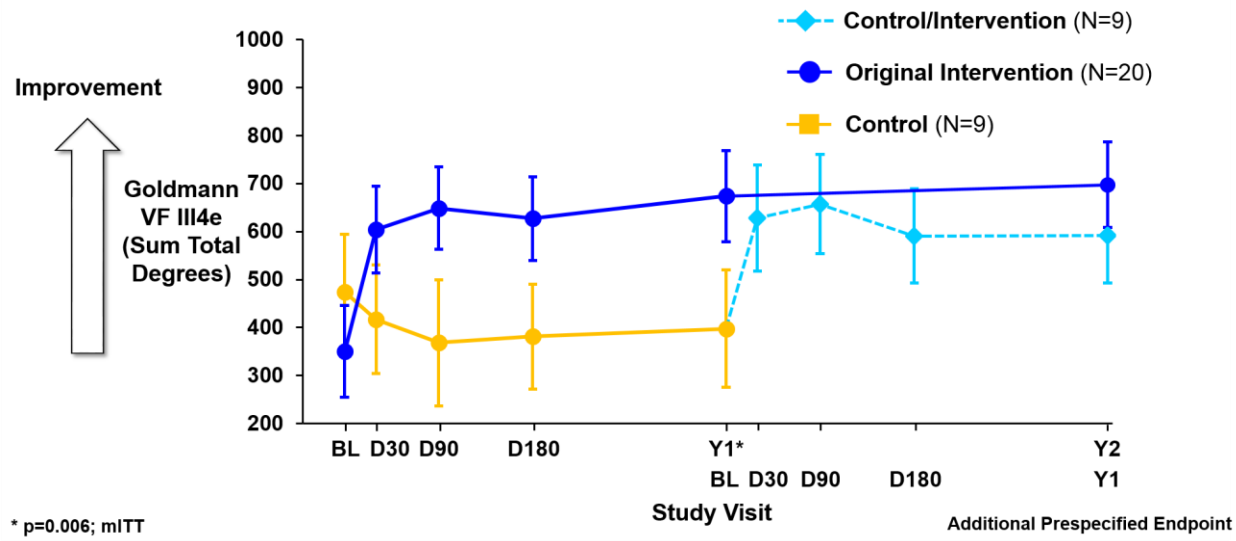


Visual fields were analyzed as pre-specified exploratory endpoints.

The Goldmann VF analysis evaluates the extent to which a subject can see from a central point of fixation, using targets (or stimuli) of varying size and brightness. Goldmann VFs were measured in sum total degrees, with a higher value representing a larger field of vision; normal individuals have Goldmann VFs of approximately 1200-1400 sum total degrees. On average, the Intervention group showed an increase of 302.1 sum total degrees compared to a reduction of 76.7 for the Control group. The mean treatment difference (95% CI) was 378.7 (145.5, 612.0) degrees (nominal p=0.006; ITT) for the Goldmann VF using the III4e light stimulus. After crossing over, the Control/Intervention group showed a mean change from injection baseline of 194.3 sum total degrees at 1 year (Figure 12).

Subjects were also evaluated using the Humphrey VF Analyzer, a computerized method that primarily tests the function in the center of the VF. Humphrey static perimetry showed a statistically significant improvement in mean macula threshold values when comparing change at Year 1 for Interventions and Controls. The mean treatment difference (95% CI) at Year 1 was 7.9 dB (3.5, 12.2) (nominal p<0.001; ITT). No statistically significant changes were noted for foveal threshold levels.

Figure 12: Observed Mean Visual Field Testing (Goldmann III4e) Over Time in Phase 3 (mITT)



Additional functional vision assessments included a visual function questionnaire (a patient reported outcome) and a community-based functional vision assessment, designed and conducted by orientation and mobility experts, which were used in the Phase 3 clinical trial to provide further insight into actual visual performance in everyday life and activities of daily living.

Overall, the Phase 3 study demonstrates that bilateral subretinal injection of voretigene neparvovec is an effective treatment option for patients suffering from vision loss due to biallelic *RPE65* mutation-associated retinal dystrophy. The pre-specified primary endpoint was statistically significant, demonstrating substantial improvement in functional vision. Voretigene neparvovec treatment also led to statistically significant improvement in visual function as measured by FST. Nominally significant improvements were also observed in Goldmann III4e and Humphrey static perimetry macular threshold VF exams.

Benefits observed throughout Year 1 in the Original Intervention group are further supported by similar results observed in Control/Intervention subjects following administration of voretigene neparvovec. Finally, improvements in both functional vision and visual function were observed for at least 2 years following administration in the Original Intervention group through the May 2016 Biologics License Application (BLA) cut-off date, suggesting a durable response.

1.5 Safety

The clinical development program included 41 subjects in whom 81 eyes were injected with voretigene neparvovec (Table 7). In total, 72 eyes were administered the proposed dose of 1.5E11 vg. Additionally, all subjects in the clinical program have been enrolled in a long-term follow-up study and will be followed for 15 years after vector administration. To date, subjects from the Phase 1 studies (n=12) have been followed for safety for seven to nine years and subjects from the Phase 3 study (n=29) for two to four years.

Table 7: Voretigene Neparvovec Exposure in Phase 1 and 3 Studies

	Voretigene Dose Cohorts (Number of Eyes Exposed)			Total Eyes Exposed	Total Subjects Exposed
Study	**1.5E10 vg**	**4.8E10 vg**	**1.5E11 vg**		
Total	3	6	**72**	**81**	**41**
Phase 1	3	6	**14**	**23***	**12**
101 (1st Eye)	3	6	3	12	
102 (2nd Eye)	-	-	11	11	
Phase 3	**-**	**-**	**58**	**58**	**29**

*One subject did not meet eligibility criteria for administration in the contralateral eye.

Table 8 shows an overview of AEs across the Phase 1 and Phase 3 studies through the safety data cut-off of 05-May-2017. Across the development program, 85% of subjects reported a maximum severity of any AE of mild or moderate intensity. Six subjects experienced severe AEs; all of these events were assessed as unrelated to voretigene neparvovec, one is resolving and all others resolved without sequelae. These severe AEs included headache (Study 102); lower limb fracture (Study 102); nausea and vomiting (Study 301); chest pain, nausea, vomiting, tachycardia and adverse drug reaction (ADR; Study 301); convulsion and ADR, convulsion (Study 301); and menorrhagia, pneumonia (Study 301).

Table 8: Summary of Adverse Events in Phase 1 and 3 Studies

Number (%) of Subjects	**Total Phase 1 (N = 12)**	**Total Phase 3 (N = 29)**	**Total Phase 1 + Phase 3 (N = 41)**
with at least 1 TEAE	12 (100%)	29 (100%)	41 (100%)
with serious TEAEs	5 (42%)	4 (14%)	9 (22%)
with TEAEs of maximum severity of			
mild	4 (33%)	10 (34%)	14 (34%)
moderate	6 (50%)	15 (52%)	21 (51%)
severe	2 (17%)	4 (14%)	6 (15%)
with TEAEs related to the vector	0	3 (10%)	3 (7%)
with TEAEs related to the administration procedure	10 (83%)	19 (66%)	29 (71%)
with ocular TEAE	11 (92%)	19 (66%)	30 (73%)

Overall, AEs following a single, one-time subretinal administration of voretigene neparvovec per eye, tended to occur early and diminish and resolve over time. As of the 05-May-2017 safety data cutoff, all subjects had experienced at least one AE. The most commonly (≥30%) occurring AEs were headache, elevated white blood cell count, fever, nasopharyngitis, nausea, vomiting and cough (Table 9).

Table 9: Commonly Occurring Adverse Events

AEs Occurring in >30% Subjects	Voretigene Neparvovec Treated Subjects	
	Phase 1 7-9 years follow-up (N=12)	**Phase 3 2-4 years follow-up (N=29)**
Any AE	**12 (100%)**	**29 (100%)**
Headache	8 (67%)	13 (45%)
Leukocytosis	6 (50%)	11 (38%)
Pyrexia	8 (67%)	9 (31%)
Nasopharyngitis	8 (67%)	8 (28%)
Nausea	4 (33%)	10 (34%)
Vomiting	3 (25%)	10 (34%)
Cough	5 (42%)	8 (28%)

There were 14 serious adverse events (SAEs) reported by nine subjects; none were assessed to be related to product, and most were unrelated to the administration procedure. Two subjects experienced ocular SAEs: one of retinal disorder (verbatim loss of foveal function), assessed as related to the administration procedure, and one of intraocular pressure increased (see Section 9.3 for detailed description) assessed as related to prior periocular steroid treatment given for an event of endophthalmitis. No deaths were reported during the clinical development program or through the long-term follow-up.

Table 10: Serious Adverse Events in Phase 1 and 3 Studies

	Voretigene Neparvovec Treated Subjects	
	Phase 1 7-9 years follow-up (N=12)	**Phase 3 2-4 years follow-up (N=29)**
Any SAE	5 (42%)	4* (14%)
Retinal Disorder	0	1
Intraocular Pressure Increased	1	0
Anal Fistula	1	0
Cryptochism	1	0
Paraesthesia	1	0
Lower Limb Fracture	1	0
Convulsion	0	1
Adverse Drug Reaction [a]	0	2
Menorrhagia	0	1
Pneumonia	0	1

*In Phase 3, one subject experienced SAEs of convulsion (3 events) and ADR, and one subject experienced SAEs of menorrhagia (2 events) and pneumonia.

[a] Includes one ADR to anti-seizure medication for a pre-existing complex seizure disorder and one ADR to anesthesia received during oral surgery.

Overall, 73% of subjects reported ocular AEs, which were identified as adverse events of special interest (AESIs). The majority of these events resolved with minimal or no intervention and without sequelae.

Adverse events of macular disorders were reported in nine eyes in seven subjects and included events of macular hole, macular degeneration, eye disorder, maculopathy, and retinal disorder (including the SAE mentioned above). Of these events, two resolved, three resolved with sequelae and four (one macular hole and three maculopathy) were unresolved at the time of data cut-off. All of the nine events were considered related to the procedure, and none were considered related to the product.

Eight subjects experienced 10 events of elevated intraocular pressure. Nine of the 10 events resolved without sequelae, and the one ongoing event is in an eye that did not receive voretigene neparvovec. Most events were considered related to the administration procedure. One event was an SAE (mentioned above, described in detail in Section 9.3) and was assessed to be due to prior periocular steroid treatment and not related to the vector or administration procedure.

Four retinal tears were reported in four subjects; all events were non-serious and resolved without sequelae. The retinal tears were observed and repaired by the surgeon with laser retinopexy during the vector administration procedures. All four events were considered related to the administration procedure and none were considered related to the product.

Three subjects experienced five AEs of intraocular infection and/or inflammation, including one event of culture-positive endophthalmitis (see Section 9.3). All five events were considered non-serious, resolved, and were considered related to the administration procedure and not to the product.

Patients with IRDs have a higher incidence of cataract formation than the general population, and vitrectomy (part of the voretigene neparvovec administration procedure) is associated with a high incidence of cataract formation and/or progression. Nine subjects reported cataracts in 16 eyes, all of which were non-serious. Seven of the 16 eyes have had elective cataract extraction procedures, and there are currently nine eyes in five subjects with ongoing events of cataracts. Most of the cataract events were considered related to the administration procedure.

Additional safety topics of interest include retinal deposits, retinal thickness measurements by OCT imaging, decreased VA, and immunology data.

In the Phase 3 study, there were three AEs of retinal deposits in one eye each in three subjects in the Control//Intervention group. In two subjects, the event was in the first eye, and in one subject the event was in the second eye. The onset of these events occurred within one to six days after administration of voretigene neparvovec. All of the events were mild in intensity, transient in nature, and resolved without intervention or sequelae within seven to 27 days. All of the events were considered to be related to the product.

In Phase 3, OCT imaging was conducted for safety assessment. Thinning of the central retina as measured by OCT imaging was noted in the post-operative period, with a mean change from Baseline in foveal thickness at Day 30 of -24.4 (from a Baseline mean of 185.2) microns. Retinal thickness returned to pre-treatment thickness by the Year 1 visit.

Across the program, and over observation periods of up to nine years, nine eyes in seven subjects had a clinically meaningful decrease in VA using the definition of a LogMAR worsening of 0.3 or more (corresponding to at least a three-line loss on an eye chart) from Baseline to the most recent visit. However, six of the nine eyes showed improvement in one or more other tests of

visual function and/or functional vision. Importantly, neither of the two Phase 3 subjects with this finding, both in both eyes, showed a worsening in bilateral functional vision by MLMT.

As voretigene neparvovec is a gene therapy product, biodistribution of vector, as well as immune responses to both AAV capsid and RPE65 protein, were analyzed. No deleterious immune responses were observed following administration of voretigene neparvovec. No clinical inflammatory responses to the investigational product have been observed, and no dose-limiting toxicity was seen in the clinical program.

In summary, the safety profile of voretigene neparvovec with follow-up for up to nine years is consistent with vitrectomy and the subretinal injection procedure. As would be expected from a single administration therapy, AEs tended to occur early and resolve over time. There were few SAEs, and none were assessed as related to voretigene neparvovec.

1.6 Conclusions

Almost all patients with biallelic *RPE65* mutation-associated retinal dystrophy will eventually progress to near total blindness that cannot be corrected by glasses or corrective surgery. There are currently no available pharmacologic treatments that can slow or stop the insidious loss of functional vision and visual function for these patients. While this blindness represents the extreme end of progression, the majority of individuals begin to experience functional vision loss before the age of 18, which can substantially limit daily life activities.

The totality of data from the clinical development program shows that voretigene neparvovec provides a clinically meaningful benefit for patients with biallelic *RPE65* mutation-associated retinal dystrophy, leading to sustained improvements in both functional vision and visual function. Voretigene neparvovec led to an improvement of 1.8 light levels in the mean bilateral MLMT score change for the Intervention group, compared to 0.2 light levels for the Control group at one year, thereby meeting the primary efficacy endpoint of Study 301. Improvements in functional vision were generally observed by 30 days post-administration, with sustained improvements through at least 2 years for the Original Intervention subjects and through at least one year for the Control/Intervention subjects.

Voretigene neparvovec has an acceptable safety profile based on up to nine years of cumulative post-administration follow-up in clinical development subjects. Overall, the voretigene neparvovec safety profile is consistent with the subretinal injection administration procedure; most of the related AEs were determined to be related to the administration procedure rather than to the gene product itself. As expected from a single exposure, most adverse events occurred early and resolved over time.

Voretigene neparvovec will be distributed solely through a small number of Centers of Excellence associated with an active ophthalmology practice that treats patients with IRDs including *RPE65* mutation-associated retinal dystrophy. Voretigene neparvovec will only be prepared and administered by healthcare professionals who have completed the in-person training program(s). A surgical training program on subretinal delivery of the product will be implemented, including an in-person multimedia presentation and wet lab hands-on training with the Principal Investigators from the program as well as a detailed surgical training manual with illustrations describing the subretinal injection procedure (Appendix 12.1). There will also be an in-person training program for pharmacists and other pharmacy personnel regarding the

preparation of the product, which will include a manual with step-by-step written instructions and illustrations as provided with the submitted labeling materials.

The Sponsor has also proposed risk management activities to monitor long-term safety of voretigene neparvovec and the administration procedure. This monitoring will include surveillance for standard gene therapy risks as outlined in the FDA long-term follow-up guidance, as well as for AEs of interest associated with voretigene neparvovec or the administration procedure. All subjects in the clinical development program have been enrolled in a long-term follow-up study in which they will be followed for 15 years post-vector administration. The follow-up study includes annual history, physical and ophthalmic examinations, blood tests, urinalysis, and retinal/visual function tests. Additionally, Spark Therapeutics plans to implement a mandatory prospective, observational safety registry to collect long-term safety data from all subjects who have been treated with voretigene neparvovec.

The overall efficacy and safety results from the clinical program demonstrated that the benefit-risk balance is strongly in favor of voretigene neparvovec for the treatment of patients with vision loss due to confirmed biallelic *RPE65* mutation-associated retinal dystrophy.

2 BACKGROUND ON BIALLELIC *RPE65* MUTATION-ASSOCIATED RETINAL DYSTROPHY

Summary

- Patients with biallelic *RPE65* mutation-associated retinal dystrophy suffer from a severe, debilitating, and progressive retinal disease. From childhood, most patients are visually compromised – eventually progressing to near total blindness in almost all patients.
- Biallelic *RPE65* mutation-associated retinal dystrophy primarily affects rod photoreceptors, while cone photoreceptors decline secondarily as the disease progresses.
- RPE65 enzyme deficiency prevents the retina from regenerating 11-*cis*-retinal, which is essential to enable conversion of light energy to an electrical signal. Build-up of toxic precursors proximal to the enzyme block leads to damage to the RPE cells; loss of RPE cells eventually leads to death of photoreceptors, accounting for the progressive nature of the disease.
- The hallmark of this disease is nyctalopia, which is the inability to see or perceive in dim light, and which manifests in both reduced visual function and functional vision. Nyctalopia is accompanied by impairment in visual field and visual acuity.
- The Natural History Study suggests there are more than 20 different clinical descriptors representing this IRD. Today, genetic testing can accurately diagnose biallelic *RPE65* mutations.
- There are no available pharmacologic treatments to address the underlying cause of the disease or delay disease progression.

2.1 Overview of Biallelic *RPE65* Mutation-Associated Retinal Dystrophy

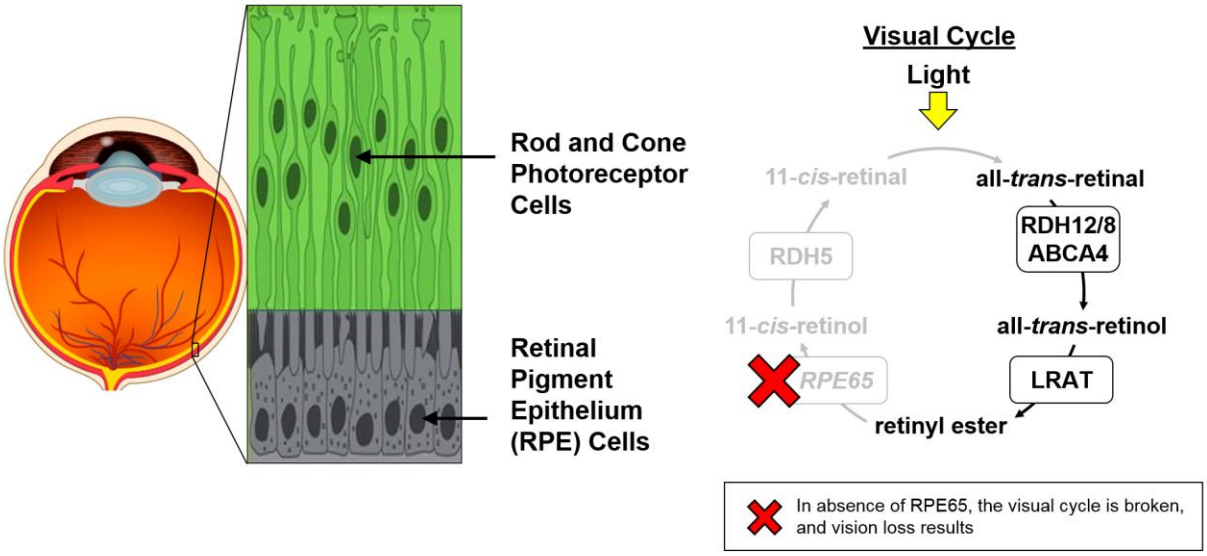
Visual perception results from the biological conversion of light energy to an electrical signal by retinal photoreceptors in the eye, namely rods and cones. While the chemical process that supports phototransduction is similar in rods and cones, rods are involved in vision at low light levels, and cones are involved in vision at higher light levels, color vision, and spatial acuity. The loss of function of rod photoreceptors is the primary cause for vision loss associated with biallelic mutations in the *RPE65* gene and manifests at early stages as decreased ability to function in reduced light conditions (Table 11). Cone photoreceptors, which affect functioning under bright light, typically decline secondarily as the disease progresses.

Table 11: Vision Loss Associated with *RPE65* Mutations

Photoreceptor Cells	Vision Loss
Rods	Nyctalopia (Inability to see/perceive in dim light) Diminished visual field Poor adaptation to suboptimal light situations
Cones	Inability to resolve finer detail Decreased ability to perceive color

The retinal pigment epithelium is a single layer of cells that form the blood-retina barrier and nourish photoreceptors (i.e., rods and cones). These RPE cells have several functions and are essential for photoreceptors to carry out their highly active metabolic requirements (Figure 13). In the visual cycle, the chromophore 11-*cis*-retinal bound to apoprotein G protein-coupled receptor opsins (rhodopsin) initiates phototransduction on the absorption of a photon, triggering photoisomerization of the chromophore to its *trans* form (Palczewski 2006; Ridge et al. 2007). The isomerized chromophore, all-*trans*-retinal, is reduced to all-*trans*-retinol and transported to the retinal pigment epithelium (RPE) where it is converted to fatty acid all-*trans*-retinyl esters by lecithin/retinol acyltransferase (LRAT). This retinoid (visual) cycle is completed by regeneration of 11-*cis*-retinal, the vitamin A derivative that contributes to the visual pigment rhodopsin, via a two-step process that is catalyzed in part by all-*trans*-retinyl isomerase (also known as the retinal pigment epithelium 65 kDa protein [RPE65]). Proper functioning of this complete cycle is critical for maintaining vision (Travis et al. 2007).

Figure 13: The Role of *RPE65* in the Visual Cycle

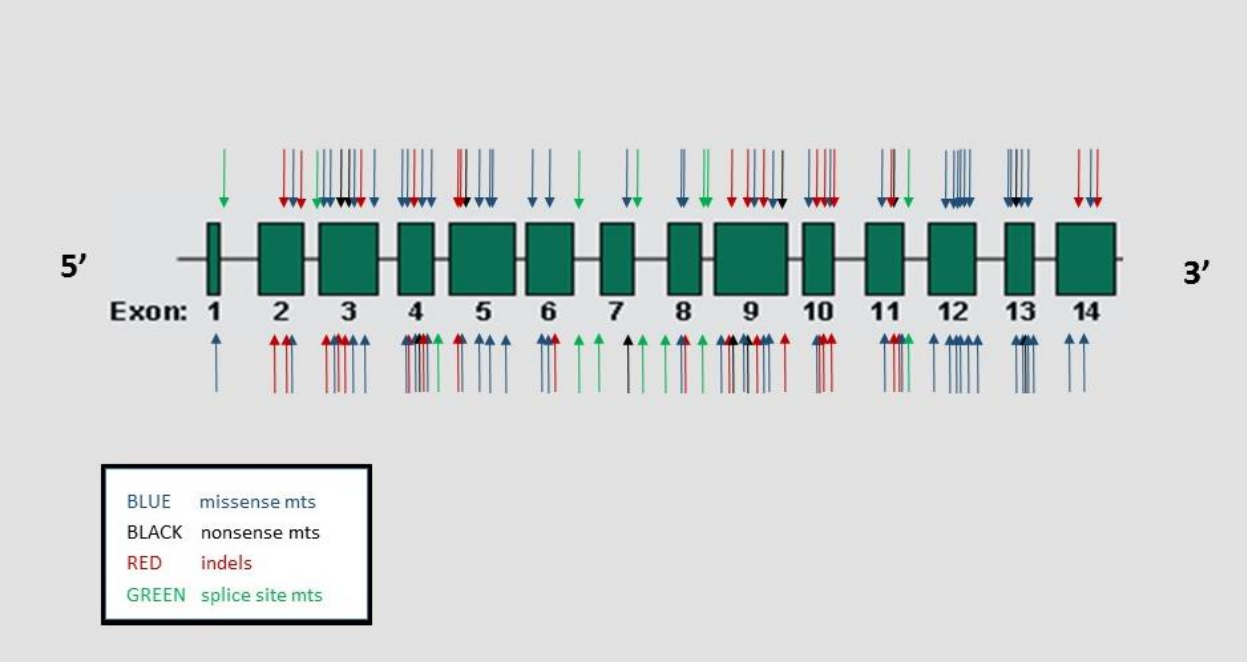


The biochemical blockade of the visual cycle resulting from RPE65 enzyme deficiency causes a profound impairment in visual function with slow but inevitable degeneration of retinal cells (Jacobson et al. 2005). The inability to regenerate 11-*cis*-retinal, via 11-*cis*-retinol, in the RPE cells impairs the ability to respond to light, and the accumulation of toxic precursors proximal to the block (caused by lack of functioning RPE65 enzyme) eventually leads to death of RPE cells, which in turn leads to death of photoreceptors (Redmond et al. 1998; Katz et al. 2001).

Replacement of the gene encoding RPE65 is predicted to lead to a gain in vision through restoration of the visual cycle.

The human RPE65 enzyme is encoded by the 20 kilobase (kb) *RPE65* gene, which contains 14 exons, interrupted by 13 introns. The protein is translated from a single mRNA transcript of 2.9 kb, resulting in a 533 amino acid protein (Nicoletti et al. 1995). Autosomal recessive mutations in this gene lead to inherited retinal degenerative disease (Redmond et al. 1998; Redmond et al. 2005). Approximately 125 discrete *RPE65* gene mutations have been reported, all resulting in pathology that is caused by a lack of functional RPE65. Figure 14 shows the loci and type of mutations in the *RPE65* gene, from patients with autosomal recessive forms of IRD reported in the literature, and from participants enrolled in the voretigene neparvovec clinical trials. The mutation types (missense, nonsense, frameshift, and splice site) and associated clinical diagnosis/historical naming conventions span the 20 kb length of the gene, which implies that there is no association of *RPE65* gene mutations in a specific region of the gene with a given clinical diagnosis.

Figure 14: Mutations in the *RPE65* Gene in Patients Enrolled in Clinical Trials of Voretigene Neparvovec and Those from the Literature by Mutation Type



Gu et al. (1997); Marlhens et al. (1998); Morimura et al. (1998); Lorenz et al. (2000); Lotery et al. (2000); Thompson et al. (2000); Simovich et al. (2001); Hanein et al. (2004); Booij et al. (2005); Stone (2007); McKibbin et al. (2010); Roberts (2010); Bowne et al. (2011); Weleber et al. (2011); Neveling et al. (2012); Verma et al. (2013); Khan et al. (2014); Wang et al. (2014)

The disease process that results from mutations in the *RPE65* gene affects mainly rod photoreceptors that mediate peripheral vision and ability to detect low luminance light. As a result, affected individuals have such decreased light sensitivity that they are night blind and have great difficulty performing activities of daily living, even under normal daytime lighting

conditions. Continued retinal degeneration inevitably includes cones as well and eventually progresses to near total blindness in almost all patients (Ferrari et al. 2011).

2.1.1 Diagnosis

Before both the identification of the underlying genetic mutations associated with IRDs and the advent of genetic testing, diagnosing the underlying genetic defect was not possible in most cases. A number of different clinical diagnoses for IRDs were assigned based on the clinical presentation including the time of onset, severity, and presenting phenotype. Patients with biallelic *RPE65* mutation-associated retinal dystrophy have been identified by many different clinical diagnoses including LCA, RP, SECORD, tapetal retinal dystrophy-LCA type, or delayed retinal maturation, among others. The ability to diagnose accurately based on genetic mutation supports a move to diagnosis using a gene-based disease classification.

2.1.2 Epidemiology

Biallelic *RPE65* mutation-associated retinal dystrophy is a rare genetic condition. Prevalence information is available for both LCA type 2 and RP type 20, the subtypes of LCA and RP due to mutations in *RPE65*. Leber congenital amaurosis (all subtypes) is estimated to affect ~1/81,000 individuals in the US (Stone 2007), or approximately 4,000 individuals based on the total population by the 2016 Census Data (~322.8 million; https://www.census.gov/popclock/). Mutations in the *RPE65* gene are identified in 8 to 16% of those diagnosed with LCA (Morimura et al. 1998; Thompson et al. 2000; Simovich et al. 2001; Stone 2007; Astuti et al. 2016), or approximately 320 to 640 individuals in the US. Retinitis pigmentosa is estimated to affect approximately 1/3,500 to 1/4,000 individuals (Fahim et al. 1993). It is estimated that a range of 1 to 3% of all patients with RP have underlying genetic mutations in the *RPE65* gene (Morimura et al. 1998; Thompson et al. 2000; Wang et al. 2014). Based on the total population by the 2016 Census Data (~322.8 million; https://www.census.gov/popclock/), this represents approximately 800 to 2,700 patients with IRD due to autosomal-recessive *RPE65* gene mutations in the US.

In total, this yields an estimated range of 1,000 to 3,000 total patients in the US with biallelic *RPE65* mutation-associated retinal dystrophy, but precise numbers have not been verified.

2.2 Current Treatment Options

There are no pharmacologic treatments available for IRD, including biallelic *RPE65* mutation-associated retinal dystrophy.

Eventually almost all patients progress to near total blindness.

2.3 Unmet Medical Need

As there are no treatments available for IRDs including the retinal dystrophy associated with mutations in *RPE65*, there is a clear need for therapy, ideally one that will address the underlying cause of this disease in order to restore the visual cycle, improve vision, and help patients function independently in their visually-dependent daily activities.

3 PRODUCT DESCRIPTION

Summary

- Voretigene neparvovec is an AAV2 gene therapy vector with a CMV enhancer, a CβA promoter and a cDNA encoding a wild-type hRPE65 protein.
- Voretigene neparvovec supplies a functional copy of a RPE65 cDNA within the RPE cells, thereby restoring the visual cycle in patients with RPE65 mutation-associated retinal dystrophy.
- Non-clinical findings in mice, dogs, and NHPs support the mechanism of action, efficacy, and safety of voretigene neparvovec for the proposed indication and dosing.
- The proposed indication of voretigene neparvovec is for the treatment of patients with vision loss due to confirmed biallelic *RPE65* mutation-associated retinal dystrophy.
- The recommended voretigene neparvovec administration regimen is sequential (within six to 18 days), bilateral subretinal injections of 1.5E11 vg delivered in a total subretinal volume of 0.3 mL per eye.

3.1 Overview of Voretigene Neparvovec

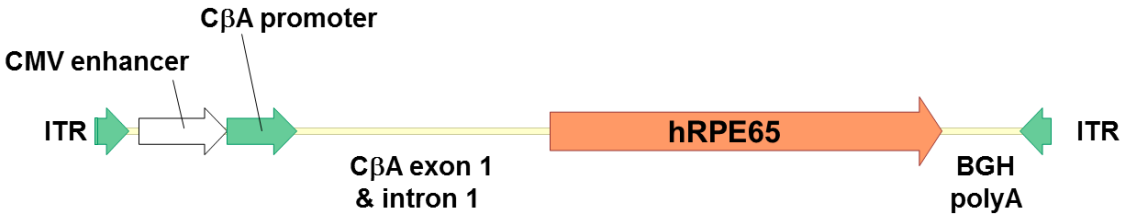
Voretigene neparvovec employs an AAV2 vector as a delivery vehicle for an expression cassette encoding normal human *RPE65*; the recombinant vector is a non-enveloped icosahedral virion of approximately 26 nanometers in diameter. The parent adeno-associated serotype 2 virus, used as a template for the vector, is a non-pathogenic, single-stranded DNA genome-containing, helper virus-dependent member of the parvovirus family.

Many studies involving AAV vectors have been conducted in a number of clinical settings, including hematologic disorders such as the hemophilias, Gaucher disease, hemochromatosis, and the porphyrias (Mingozzi et al. 2013). At least one AAV product (alipogene tiparvovec; Glybera) has been approved by the European Medicines Agency (EMA) for lipoprotein lipase deficiency (CHMP 2012).

Adeno-associated viral vectors have been administered to hundreds of participants in dozens of clinical studies at doses of up to approximately 1E15 vg or more for systemic administration (Mingozzi et al. 2011). The AAV vector payload is stabilized predominantly in a non-integrated form, reducing risk of insertional mutagenesis.

The expression cassette of voretigene neparvovec contains a CMV enhancer and a chicken β-actin promoter driving expression of a cDNA encoding a wild-type hRPE65. The construct contains an optimized Kozak sequence. A schematic representation of the voretigene neparvovec expression cassette is presented in Figure 15.

Figure 15: Schematic Representation of the Voretigene Neparvovec Expression Cassette



Voretigene neparvovec is formulated as a sterile concentrate (requiring a 1:10 dilution prior to administration) for solution for subretinal injection containing 5E12 vg per milliliter (mL).

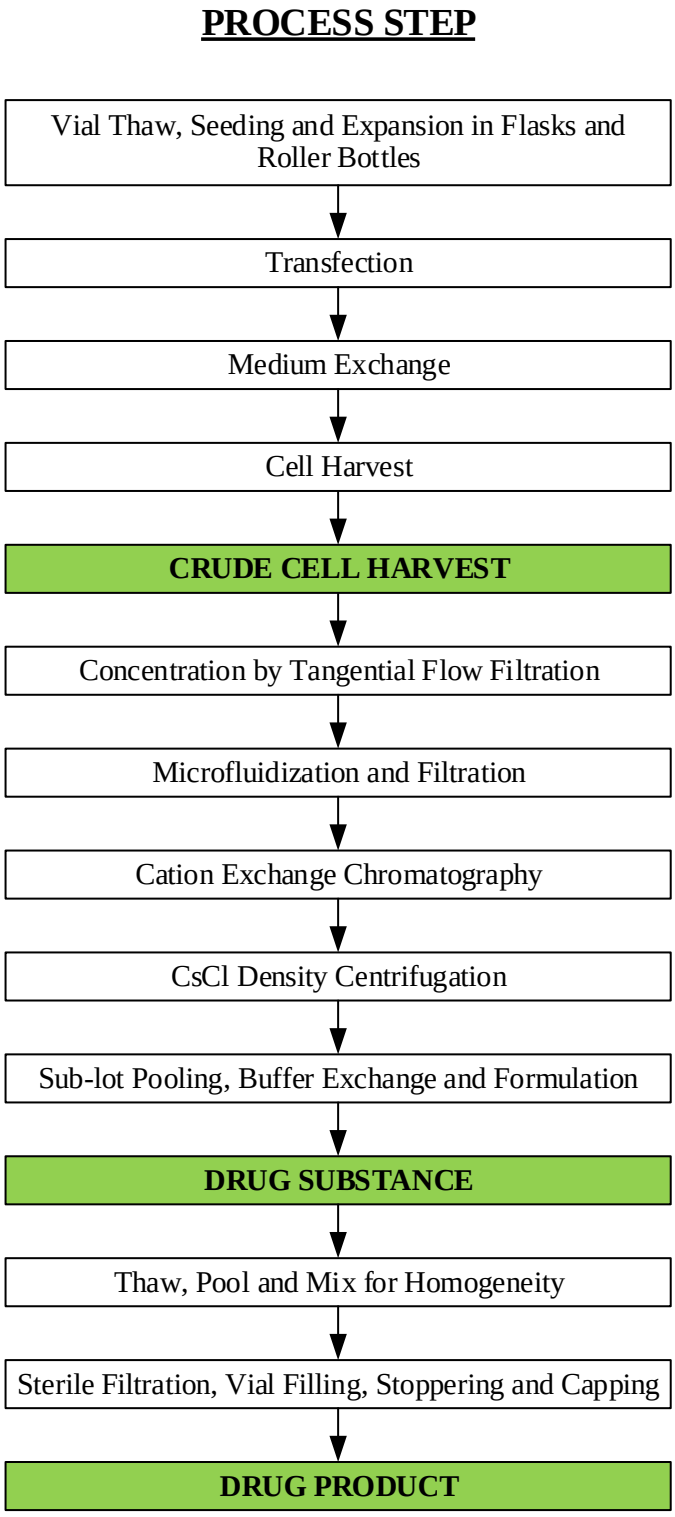
3.2 Mechanism of Action

As explained in Section 2.1, mutations in the *RPE65* gene prevent the retina from regenerating 11-*cis*-retinal, which is essential to convert light energy to an electrical signal that is transmitted through the optic nerve to the visual cortex. The mechanism of action of voretigene neparvovec is gene augmentation to express the normal, functional RPE65 protein in the RPE cells of the retina to enable restoration of the visual cycle. AAV2 vectors efficiently transduce RPE cells, making AAV2, the capsid with which there is the greatest clinical experience, the best choice for this product candidate. Additional supportive data on the mechanism of action are presented in Section 3.4.

3.3 Manufacturing

Voretigene neparvovec is manufactured using triple transfection of HEK293 cells. The downstream purification process separates empty AAV capsids from full AAV capsids, and primarily full particles are administered in the final product, which is formulated in a physiologic buffer containing a surfactant to help prevent loss of vector on product contact surfaces. An overview of the manufacturing process is presented in Figure 16. There are 40 release tests in place to ensure that each lot of voretigene neparvovec meets pre-defined criteria for safety, purity, and potency.

Figure 16: Voretigene Neparvovec Manufacturing Process Flow Diagram

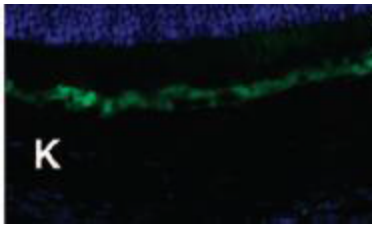


3.4 Non-clinical Findings

Pharmacology and toxicology studies conducted in mice, dogs, and NHPs demonstrate that voretigene neparvovec can be safely delivered to the subretinal space where it transduces RPE cells in the surgically targeted area, resulting in production of RPE65 protein, and providing rescue of vision in affected animals (Acland et al. 2001; Dejneka et al. 2004; Acland et al. 2005; Jacobson et al. 2005; Jacobs et al. 2006; Bennicelli et al. 2008; Amado et al. 2010). In mouse models of *RPE65* deficiency, significant improvements in visual acuity were observed in eyes treated with voretigene neparvovec. Consistent with the improvements in retinal and visual function, RPE65 protein was found localized to the RPE cells, but not other retinal cell types. A dose-dependent increase in isomerohydrolase activity (Moiseyev et al. 2003) was demonstrated in eyecups isolated from affected mice following administration of voretigene neparvovec as early as 30 days post-treatment. Administration of voretigene neparvovec was correlated with improvements in visual function, as measured by ERG. These data confirm the predicted mechanism of action of voretigene neparvovec; i.e. conversion of all-*trans*-retinol to 11-*cis*-retinol, resulting in recovery of the visual cycle.

In affected dogs, AAV2 vectors expressing either human or canine *RPE65* at doses of 1.5E10 to 1E12 vg/eye in volumes of 0.1-0.2 mL resulted in stable recovery of retinal function, as evaluated by ERG. In addition, recovery of the visual cycle, as demonstrated by detection of 11-*cis*-retinal in the treated areas, confirmed the mechanism of action of this treatment in the dog model of the disease. Immunofluorescence staining of dog eyes administered voretigene neparvovec at doses of 8.25E10 or 1.5E11 vg/eye in a volume of 0.15 mL showed that the RPE65 protein was localized to the RPE, and only in the region that had been exposed to the vector (Figure 17). These animals demonstrated significantly improved navigation and pupillary light responses, decreased frequency of nystagmus, and improved ERGs and visual behavior. Expression of *RPE65* was observed for up to 10 years following AAV-*RPE65* vector administration, with durable visual functional improvements (Cideciyan et al. 2013).

Figure 17: Detection of RPE65 in Dog Eyes Exposed to Voretigene Neparvovec



RPE65 protein immunofluorescence (green) in AAV-treated (K and left half of L) but not untreated (right half of L) RPE. Scale bars, 100 mm. Nuclei are stained blue. gcl, ganglion cell layer; inl, inner nuclear layer; onl, outer nuclear layer; rpe, retinal pigment epithelium (adapted from Figure 1 of Amado et al. (2010)).

Safety studies performed in dogs and NHPs evaluated both local and systemic toxicity. No definitive vector-related adverse effects were observed in non-ocular tissues. However, pathologic findings were observed by ocular histopathology in the eyes of dogs following subretinal administration of a precursor of voretigene neparvovec at a dose of 1.5E12 vg/eye. Inflammation was localized predominantly to the subretinal injection site, where it caused focal retinal degeneration. The inflammation predominated in the sub-RPE, choroid, tapetum, and subretinal space and appeared directed toward the RPE cell layer, which was completely absent in the inflamed areas. Given that this vector expressed low levels of RPE65, it was concluded that the observed toxicity is likely due to the high dose (10-fold higher than proposed therapeutic dose) of AAV2 capsid, and not from expression of the RPE65 protein.

Non-human primates are the most appropriate animal model to evaluate safety, for both anatomical and immunologic reasons. Ocular histopathological findings in NHPs administered 3E11 vg/eye or 7.5E11 vg/eye of voretigene neparvovec were mild, not dose-dependent and mostly attributable to surgical trauma. Thus, the no-observed-adverse-effect-level (NOAEL) is defined as 7.5E11 vg/eye, which is five-fold higher than the proposed therapeutic dose of voretigene neparvovec.

There was no evidence of a pro-inflammatory T-cell response to the AAV2 capsid or RPE65 protein in the NHP model, and a limited T-cell response to human RPE65 was observed in dogs. Antibodies to RPE65 were only detected in isolated cases, either transiently or where negative serum sample controls were also positive. Antibodies to AAV2 capsid proteins were variously detected in the anterior chamber fluid or serum of both normal and affected dogs and in NHPs previously exposed to AAV2.

Since the patient population for this treatment was to include children, safety and efficacy testing was conducted in juvenile mice and dogs. No vector-related adverse effects were observed in juvenile animals. One consideration when treating children with gene therapy is the potential for proliferation of the exposed cell types. However, the available data suggest that at birth there is little, if any, cell division occurring in neural retina cells and RPE cells (La Vail et al. 1991; Gelatt 2014). Thus, at the time of vector administration, RPE and retinal cells are unlikely to be proliferating, and thus the vector will stably transduce post-mitotic cells, enhancing efficacy and minimizing the risk for integration (Deyle et al. 2009). Overall, the data support the safety of the subretinal delivery of AAV in young children.

In summary, the findings from the pharmacology and toxicology studies support the proposed mechanism of action, as well as the safety and efficacy of voretigene neparvovec as a gene transfer approach for the treatment of patients with vision loss due to confirmed biallelic *RPE65* mutation-associated retinal dystrophy. The dose-ranging studies in animals provided evidence of efficacy at the selected dose, and of toxicity at higher doses (10-fold higher than those used in the clinical studies), and thus helped to define safe doses for clinical testing.

3.5 Biodistribution and Viral Shedding

3.5.1 Biodistribution in Non-Clinical Studies

Biodistribution of voretigene neparvovec following subretinal administration was determined by evaluating the biodistribution and shedding of vector sequences to tissue and ocular fluids,

respectively. Biodistribution was assessed using a qPCR method at three weeks and three months post-injection in normal dogs and at 3 months post-injection in NHPs. Vector DNA was observed in anterior chamber and vitreous fluids of vector-injected eyes at levels that were several logs higher than other tissues at three weeks and three months post-injection. No vector was seen in critical organs such as brain, heart, lungs, and gonads, and weak signals were observed in optic nerves and optic chiasms. Thus, subretinal administration of AAV2-hRPE65 vectors results in minimal dissemination of vector outside the ocular space. When vector sequences were seen, there was a dose-dependent and time-dependent nature to the biodistribution, with lower levels of vector observed at lower doses and at longer timepoints, suggesting vector clearance is taking place during the three-month observation periods.

3.5.2 Viral Shedding in Clinical Studies

Across studies, voretigene neparvovec vector shedding into either tears or peripheral blood appeared to be transient in nature, with the majority of positive samples occurring between one and three days after vector administration. During this three-day window, vector shedding tended to be localized to tear samples from the injected eye, though there were also positive peripheral blood samples. There was also a low number of positive tear samples for the uninjected (or previously injected) eye.

In the Phase 3 study, the shedding of voretigene neparvovec vector DNA sequences to blood and tears from both eyes was determined using a validated qPCR method. Samples were tested for the first year post-vector administration. In 13 of 29 (45%) subjects in the study, voretigene neparvovec vector DNA sequences were detected in tear samples; most of these subjects were negative after Day 1 post-injection; however, five of these subjects had positive tear samples beyond the first day, with one subject remaining positive up to Day 14 post-second eye injection. Vector DNA sequences were detected in the serum in three of 29 (10%) subjects, including two subjects with positive tear samples, up to Day 3 following each injection. Vector DNA was not detected in any whole blood samples. Overall, transient and low levels of vector DNA were detected in tear and occasional serum samples from 14 of 29 (48%) Phase 3 subjects. Similar results were observed for the Phase 1 studies; however, differences in voretigene neparvovec dose and administration (i.e., unilateral administration or non-simultaneous administration vs. near-simultaneous, bilateral administration), and the relatively small Phase 1 sample size, limit direct comparison with the Phase 3 results.

Because minimal shedding was detected in blood, it is unlikely that vector DNA would be detectable in bodily fluids such as urine or feces. Furthermore, the presence of voretigene neparvovec copies in blood does not mean that there is vector capable of transducing a cell; the levels that were detected are well below what would be required for a transduction/infectivity assay. Therefore, collection and analysis of urine and feces was not deemed necessary in the Phase 3 study.

3.6 Proposed Indication

In 2014, voretigene neparvovec was granted Breakthrough Therapy designation for treatment of nyctalopia in patients with LCA due to *RPE65* mutation.

With the advances in genetic diagnoses, and based on the mechanism of action, Spark Therapeutics is seeking approval of voretigene neparvovec for the treatment of patients with vision loss due to confirmed biallelic *RPE65* mutation-associated retinal dystrophy.

The product should only be administered to patients with sufficient viable retinal cells, which can be estimated by OCT as an area of retina within the posterior pole of greater than 100 micron thickness.

3.7 Regulatory History

The initial IND for voretigene neparvovec was submitted to FDA in June 2007 to assess the safety and tolerability in subjects with LCA due to confirmed biallelic RPE65 mutations. Orphan product designations of voretigene neparvovec were granted for the treatment of LCA due to *RPE65* mutations in June 2008 and for treatment of RP due to autosomal recessive *RPE65* gene mutations in March 2015. Based on the evolution of genetic disease diagnosis and treatment, the orphan designation was later amended for the treatment of IRD due to biallelic *RPE65* mutations, which is in line with the proposed indication (Section 3.6).

In June 2011, the FDA held an Advisory Committee meeting to discuss cellular and gene therapy trials for the treatment of retinal disorders. A key conclusion from this meeting was the need for novel endpoints tailored to disease and clinical deficit. Additionally, the committee recommended the use of multiple tools that can measure visual function and functional vision, as well as consideration of patient reported outcomes related to activities of daily living. These recommendations, in addition to inputs from multiple discussions and meetings with FDA, were incorporated into the design of the voretigene neparvovec development program.

Spark Therapeutics received Breakthrough Therapy designation for voretigene neparvovec in September 2014 and a Rare Pediatric Disease Designation in July 2017.

As noted in Section 3.6, the proposed indication for voretigene neparvovec is for the treatment of patients with vision loss due to confirmed biallelic *RPE65* mutation-associated retinal dystrophy, which may be described clinically as LCA, RP, or other similar clinical descriptors. The therapeutic indication encompasses the spectrum of IRD resulting from autosomal recessive mutations in the *RPE65* gene and the broad range of mutations that have been studied in the clinical trials with voretigene neparvovec. The indication is also supported by the Natural History Study (Section 7) and Phase 1 and Phase 3 studies (Sections 8.1 and 8.2, respectively). Importantly, the mechanism of action for voretigene neparvovec – recovery of biochemical activity of the RPE65 protein, and thus the retinoid cycle, by gene augmentation – is dependent on the confirmed genetic diagnosis and the presence of sufficient viable retinal cells rather than the clinical descriptor.

3.8 Dosing and Administration

To ensure an optimal experience for each patient, the product will be administered in a limited number of medical centers, with ready access to medical retina specialists with expertise in IRDs including *RPE65* mutation-associated retinal dystrophy, vitreoretinal surgery expertise, and pharmacies adequately trained to handle the product with all staff having successfully completed specific training provided by Spark Therapeutics on product handling and administration.

The recommended voretigene neparvovec administration regimen is sequential, bilateral subretinal injections of 1.5E11 (or 150 billion) vg delivered in a total subretinal volume of 0.3 mL per eye. The individual administration procedures to each eye are to be performed on separate days no more than 18 days (12 days ± 6 days) apart. The six to 18-day interval between administrations was used in Phase 3 to afford an opportunity for identification of early-emergent potential surgical complications prior to a patient undergoing the second procedure, and to reduce the risk of a deleterious immune response by carrying out the two administration procedures in a near-simultaneous fashion, rather than a more widely spaced interval that could facilitate a prime boost response.

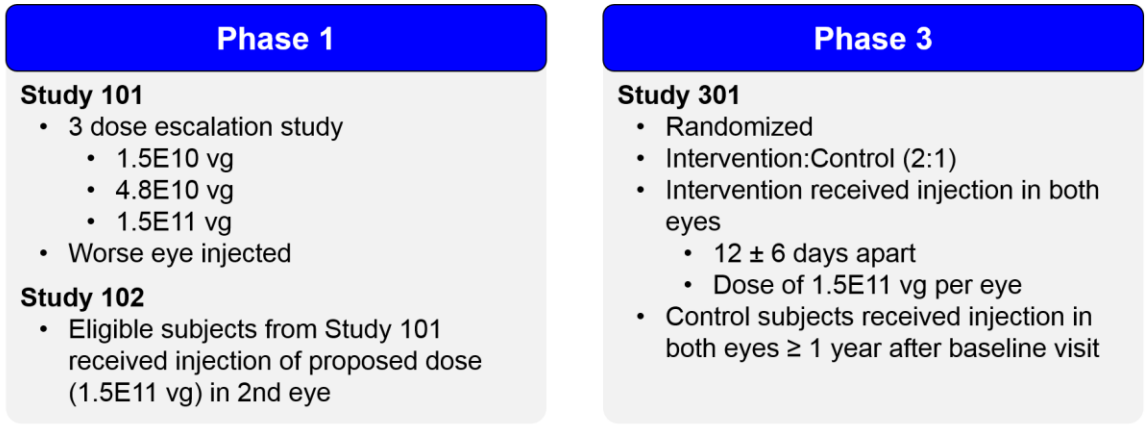
An area for injection was identified based on clinical examination and non-invasive testing such as OCT and/or visual fields. Approximately one-fourth to one-third of the total retinal area was targeted, and selected carefully to maximize the potential that viable retinal cells were exposed to the vector.

4 DEVELOPMENT HISTORY

4.1 Clinical Development Program

The voretigene neparvovec clinical program included 43 patients with *RPE65* mutation-associated retinal dystrophy, of whom 41 were exposed to a range of doses of voretigene neparvovec. Three clinical studies were conducted (Figure 18): two open-label Phase 1 studies (Study 101 and Study 102) and one open-label, randomized, controlled Phase 3 study (Study 301, with crossover from control to intervention after 1 year).

Figure 18: Voretigene Neparvovec Development Overview



Studies 101 and 102 were Phase 1 studies designed primarily to assess the safety and tolerability of subretinal administration of voretigene neparvovec, and secondarily to evaluate a number of clinical measures of efficacy in human subjects. Study 101 was a dose-escalation study in which the worse of the two eyes of eligible subjects (n=12) was identified and administered one of three doses: 1.5E10, 4.8E10, or 1.5E11 vg. Study 102 was a follow-on study in which eligible subjects from Study 101 (n=11) underwent administration of 1.5E11 vg voretigene neparvovec in the contralateral eye after at least one year of follow-up on the initial study.

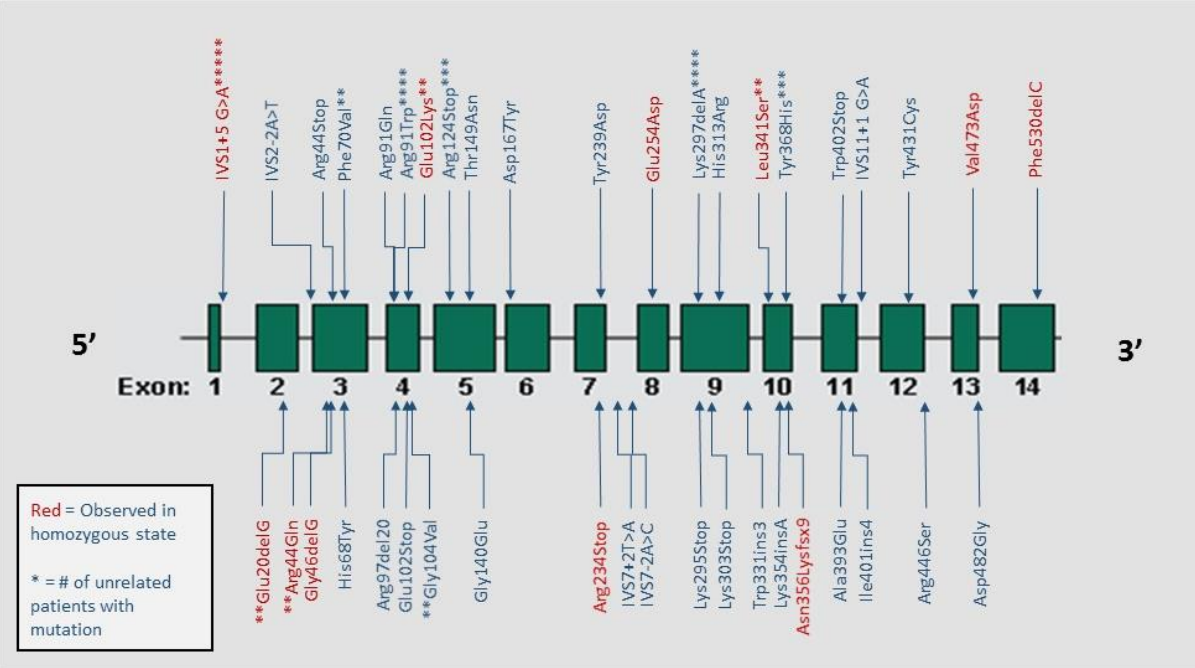
Study 301 was an open-label randomized controlled Phase 3 study in which subjects with confirmed biallelic *RPE65* mutations were randomized in a 2:1 fashion to either the voretigene neparvovec (1.5E11 vg) or Control group and followed for one year. Since the clinical trial included pediatric subjects, sham surgeries/injections were not performed in the Control group. After completion of one year of observation, Control subjects were allowed to cross-over and receive voretigene neparvovec treatment (referred to as Control/Intervention subjects after crossover and administration).

4.1.1 Genetic Diagnoses

To be included in the voretigene neparvovec clinical trials, subjects were required to have molecular diagnosis of confirmed biallelic *RPE65* mutation-associated retinal dystrophy; both homozygotes and compound heterozygotes were eligible. Thirty-four unique genetic diagnoses

were represented among the 41 subjects who have received voretigene neparvovec, including four pairs of siblings. The location of the discrete *RPE65* gene mutations (each allele separately, with those observed in a homozygous state noted in red) for trial participants is shown in Figure 19. These mutations were compared with mutations in the *RPE65* gene from patients with autosomal recessive forms of IRD reported in the literature in Figure 14 in Section 2.1.

Figure 19: Location of the Mutations in the *RPE65* Gene in Patients Enrolled in Clinical Trials of Voretigene Neparvovec



4.1.2 Injection Procedure

Subjects in the Phase 3 Study 301 received a single dose of voretigene neparvovec by subretinal administration to each eye using a standardized procedure optimized during Phase 1 and detailed below. In addition to standard preoperative and postoperative procedures, an immunomodulatory regimen of oral prednisone/prednisolone was initiated prior to subretinal injection and tapered off shortly thereafter.

The proposed administration of voretigene neparvovec consists of pars plana vitrectomy and subretinal injection conducted in the surgical suite under controlled aseptic conditions. The administration procedure was standardized during the clinical trials and further refined in order to deliver voretigene neparvovec safely into the subretinal space. The surgeon performs the following six steps:

1. Conduct a standard 3-port pars plana vitrectomy.
2. Inspect the macula and remove remaining attached vitreous and visible epiretinal membrane if present.
3. Select injection site.

4. Inject voretigene neparvovec into subretinal space.
5. Perform a fluid-air exchange in the vitreous cavity to provide tamponade and remove excess voretigene neparvovec that may have refluxed during subretinal injection.
6. Close incisions.

For more details of the procedure (including the immunomodulatory regimen), the Surgical Training Manual can be found in Appendix 12.1.

4.1.3 Clinical Evaluation Methods

At the time of initiation of the voretigene neparvovec clinical development program, there was little precedent for testing the effects of therapy in individuals with inherited retinal dystrophies. To provide context, it is helpful to note that visual function tests measure how the *eyes* function; these may include visual acuity, visual fields, and other measures, and are typically measured in each eye separately. Functional vision, on the other hand, measures how a *person* functions in a visually dependent activity, and may in a sense be considered a performance output of visual function. Functional vision is usually measured by person, not by eye, and has typically been assessed in a qualitative rather than quantitative fashion.

The investigators sought early on to develop the methodology for assessing functional vision relevant for the vision loss experienced by patients with *RPE65* mutation-associated retinal dystrophy (Chung et al. 2017). As such, an early, exploratory version of mobility testing was included as an additional assessment in Study 101 to analyze changes in functional vision. The mobility test was optimized and refined during Study 102 and was further characterized in the Mobility Test Validation Study (Chung et al. 2017). A standardized version was subsequently utilized as the primary endpoint in the Phase 3 study. The MLMT endpoint was developed to measure functional vision in a quantitative manner at light levels commonly encountered during activities of daily living. Details on the endpoint can be found in Section 5.

Nyctalopia, or a decreased ability to perceive and/or see in dim light, can be evaluated by both tests of visual function (e.g., FST) and tests of functional vision (e.g., MLMT). For both visual function and functional vision, there is a broad range of performance within the target population, with a continuum of vision loss. Thus, the overarching goal of selecting and optimizing the efficacy endpoint during the voretigene neparvovec clinical development program was to capture subjects' visual function and functional vision in a quantifiable manner, over a wide range of parameters, in order to have a comprehensive assessment of both subjects' clinical presentation (range of functioning or vision loss) and treatment response following administration.

Detailed information on the visual tests used in the voretigene neparvovec development program can be found in Section 6 and Appendix 12.2. It should be noted that, given the mechanism of action of the investigational agent and the known time course of expression from an AAV2 capsid, the prediction was that clinically detectable improvement would be observed within four to six weeks of vector injection.

5 MULTI-LUMINANCE MOBILITY TEST ENDPOINT

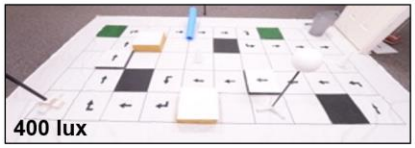
Because traditional mobility metrics do not address the effects of illumination on speed and accuracy of navigation in a standardized and quantitative manner (Thompson et al. 2015), Spark Therapeutics developed a novel mobility test assay for the efficacy evaluation of voretigene neparvovec. The final version of the MLMT endpoint used in Phase 3 (described in Section 5.1) was based on data collected in the Phase 1 studies and input from the FDA. To ensure additional rigor and objectivity, the test was also validated in the MTVS (see Section 5.4) concurrent with the Phase 1 Studies to evaluate content and construct validity (Chung et al. 2017).

5.1 Multi-Luminance Mobility Test

The multi-luminance mobility test was designed to measure changes in functional vision, specifically the ability of a subject to navigate a course accurately and at a reasonable pace at different levels of environmental illumination. The test uses seven standardized levels of illumination ranging from 1 lux to 400 lux, verified with calibrated light meters at five different positions on the course (Table 12). Performance on the test depends on the subject's visual acuity, visual field, and the extent of nyctalopia, each of which are functions specifically affected by *RPE65* mutation-associated retinal dystrophy.

Table 12: Light Levels for Multi-Luminance Mobility Test

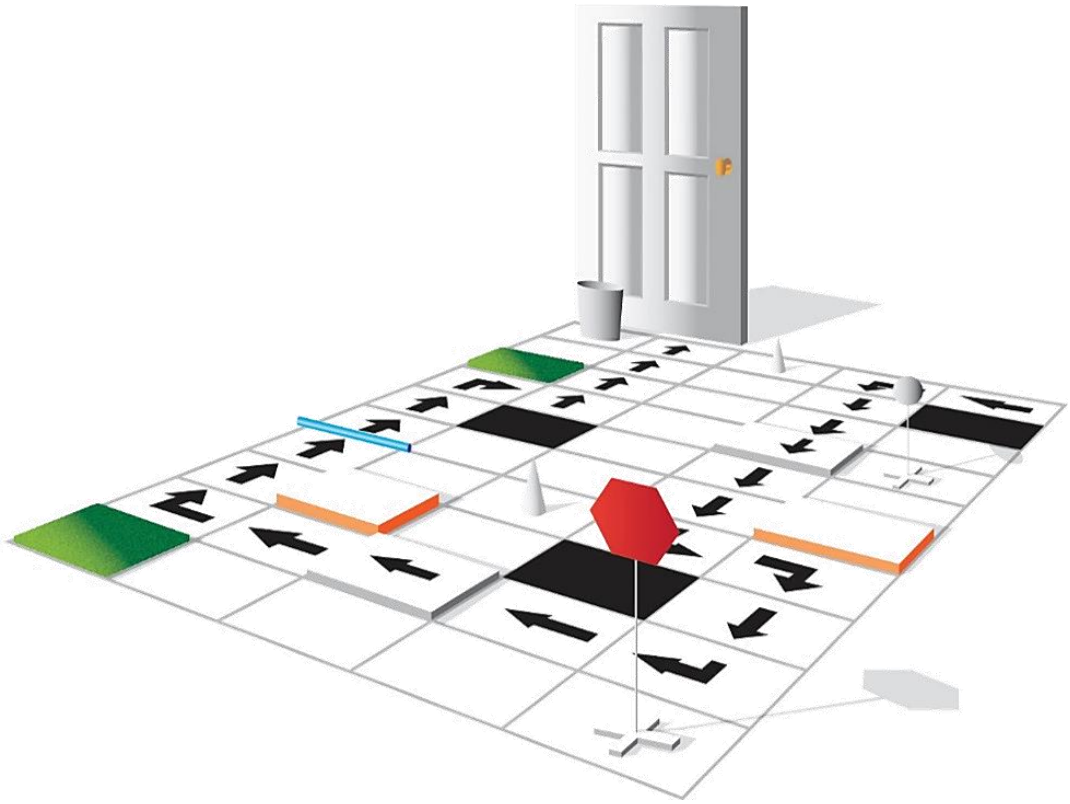
Light Levels	Examples
1 lux	Moonless summer night; Indoor nightlight
4 lux	Cloudless night with half moon; Parking lot at night
10 lux	1 hour after sunset in city; Bus stop at night
50 lux	Outdoor train station at night; Inside of lighted stairwell
125 lux	30 minutes before sunrise; Interior of train / bus at night
250 lux	Interior of elevator or office hallway
400 lux	Office environment or food court



Light meter: National Institute of Standards and Technology-calibrated,
Extech model #EA33 light meters used to provide examples and to set / verify specified light levels used for mobility testing

The MLMT consists of 12 different mobility courses each measuring 5' x 10' (Figure 20). The path to be traversed is indicated with printed black arrows standardized to dimensions consistent with Snellen lettering for VA of 20/200 at two meters. Each course is standardized for number of turns and number and type of obstacles.

Figure 20: One of 12 MLMT Course Configurations



Following 40 minutes of dark adaptation, participants complete the course with one eye patched, then complete a new configuration with the other eye patched, and then perform the test using a third configuration with neither eye patched. Each test run of a subject, at differing light intensities and on randomly selected courses, is videotaped. The videotapes are coded, transferred to an independent reading center, and assessed by two graders who are masked to the subject's treatment assignment and study visit, using a defined combination of speed and accuracy scores. At baseline, participants complete at least two practice runs (first without any eye patching and then with one eye patched, at 250 lux) on a separate training course before being scored, with more practice runs allowed if necessary for comprehension. The same training or practice course was used for all subjects, but was not used in actual testing. Practice runs were not submitted for independent scoring.

The following parameters are assessed on each course: number of obstacles hit, number of times off-course, number of times re-guided, number of tiles bypassed, and time to course completion. From these data, obstacles plus penalties were calculated, as well as an accuracy score, course time, and time score. The graders assign each course completion either a "pass" or "fail," depending on whether the subject can navigate the course within a fixed time limit (180 seconds in Phase 3) and with a minimum number of errors (three in Phase 3) at the light level being tested. The time score is determined by combining the seconds to complete the course with time penalties (i.e., 15 seconds added for each instance off course; 15 seconds added for each tile bypassed; and 30 seconds added for each redirect). The accuracy score, which is more intuitively

described as an error score (i.e., the higher the accuracy score, the more errors), is calculated by dividing the number of accuracy penalties by the total number of obstacles.

This process is repeated until failing and passing levels are identified for each eye-patching condition, progressing from lower to higher light levels.

To quantify subject performance over time in the Phase 3 study, each of the seven light levels was assigned a lux score ranging from 0 to 6 (Table 13). The MLMT score change was determined using the difference in lux scores for the lowest light level passed (Year 1 - Baseline). A positive score change reflects passing the MLMT at a lower light level, and a lux score of six (passing at 1 lux) at Year 1 represents the maximum possible MLMT score change.

Table 13: MLMT Light Levels and Lux Scores

Light Level	MLMT Lux Score
1 lux	6
4 lux	5
10 lux	4
50 lux	3
125 lux	2
250 lux	1
400 lux	0

5.2 Clinically Meaningful Change on MLMT

A change of one light level in passing the MLMT was considered clinically significant, especially against the backdrop of the progressive nature of this condition. Improvements in the ability to navigate more quickly and more accurately at lower light levels than previously possible increases an individual's safety and independence. The lighting levels selected and utilized for MLMT testing span a range that is routinely encountered in everyday situations, such as walking to class or through an office building, crossing streets at dusk, playing outside, or locating objects in dimly lit conditions. Generally speaking, the ability to safely navigate in dimmer conditions than previously possible opens up a wider range of potential opportunities for a patient and expands the environments in which they can safely and efficiently function independently, including college students who are now able to take night classes, children who are able to play outside longer when it gets dark, and adults who can independently commute to their job, go shopping at night, dine in dimly lit restaurants, or get a glass of water during the night.

As a specific example, 125 lux is equivalent to the interior of a bus or train at night and 50 lux is the brightness of an indoor stairwell or outdoor train station at night. While an individual might be able to safely navigate a train car (125 lux) for a commute at night, more difficulty might be encountered at an outdoor train station at night (50 lux), which could preclude the independent

use of that method of transportation, and limit the mobility of the individual. An improvement of one light level (125 lux to 50 lux) would allow the individual to independently use the train for their commute. This change represents a positive impact on an activity of daily living and a clinically meaningful improvement.

5.3 Evolution of Mobility Testing from Phase 1 to Phase 3

Mobility testing began as an exploratory endpoint in Phase 1 and evolved throughout Studies 101 and 102. During Study 101, the mobility testing protocol was expanded to include testing under a range of lighting conditions. Courses were standardized to contain a specified number of turns and specified numbers of specific obstacles. The videotaping protocol was refined thereby enabling more accurate scoring of the tests by analyzing collisions, times re-guided back onto the course, times that arrows were bypassed, etc. To ensure objective grading, the videotapes were transferred to an independent reading center for grading. The graders were masked to treatment group and study visit, and videotapes were presented in shuffled order, so that a grader might first see a tape from day 180 and subsequently view the Baseline tape from the same subject.

Based on input from the FDA, as well as the results of the Mobility Test Validation Study (MTVS; Section 5.4), mobility testing was further refined and standardized as described below (Section 5.3.1).

5.3.1 Standardization

To optimize and ensure greatest consistency of mobility testing procedures, the following changes were implemented during the standardization process and prior to Phase 3 study conduct:

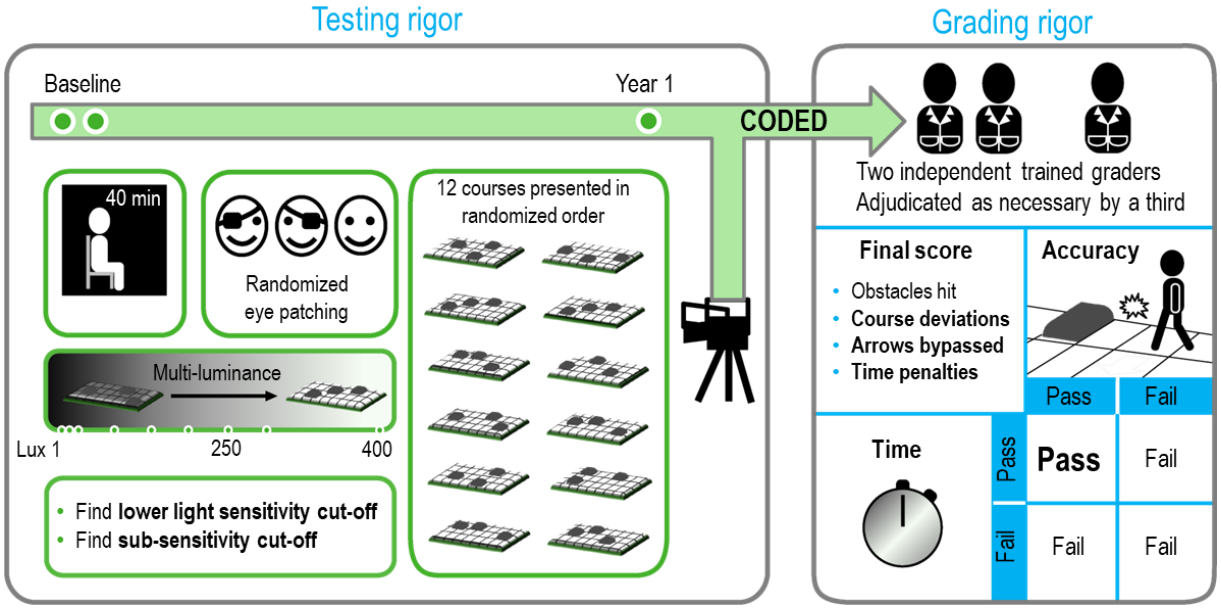
- Testing was to be carried out at Baseline to determine the lowest light level (for each eye and for the bilateral testing condition) at which a subject could carry out mobility testing with sufficient speed and accuracy to achieve a (pre-defined) passing score.
- The number of standardized light levels was decreased from nine to seven for Phase 3 in order to show a greater distinction in subjects' performance between the testing levels.
- Lighting was installed professionally in a dedicated space, and lux levels were confirmed using calibrated instrumentation before each day's runs.
- The courses were standardized so that both intra-subject and inter-subject test results could be compared more accurately.
- To reduce the learning effect, twelve different test configurations were devised, keeping distance, number of turns, and number of obstacles constant. Tests were presented in a randomized order at assessment visits.
- Procedures with which to document (videotape) the test performance were optimized.
- Following transfer to an independent reading center, each video was graded by two masked graders, trained in orientation and mobility, with adjudication by a third masked grader if they did not agree.

- Graders were trained by orientation and mobility experts, to identify kinesthetic and tactile inputs vs. visually-guided movement through the mobility course.
- Graders were instructed to monitor examiner conduct in the mobility course runs, to provide quality assurance.
- Detailed instructions as to how to carry out Baseline and subsequent mobility testing and scoring were assembled into a standard operating procedure.
- The scoring paradigm was finalized, namely weighting the accuracy and speed for each test according to a defined algorithm that places greater emphasis on accuracy than speed, including accuracy and time penalties (essentially required the timely and accurate completion of the course).
- Ten percent of videotapes from each quarter were resubmitted for grading, to provide statistics on grade-regrade concordance.

Data using the MLMT from the Phase 1 and Phase 3 studies and the Mobility Test Validation Study showed high inter-observer, test-retest, and intra-observer reproducibility in test scoring of >4000 videotaped runs from the clinical development program (see Section 8.2.1.3 for more details).

Figure 21 shows an overview of the testing and grading procedures for the MLMT.

Figure 21: Mobility Testing Assessment



5.4 Mobility Test Validation Study (MTVS)

To support the use of MLMT as the primary efficacy endpoint for the pivotal Study 301, the MTVS was conducted to determine whether a mobility test, carried out at a series of specified light levels selected to span lighting conditions that individuals encounter in daily life, could

detect changes over time in functional vision in subjects with IRDs and thus serve as a tool to assess natural history and potential benefit of investigational agents.

5.4.1 Study Design

Study MTVS was a prospective, observational study evaluating subjects' ability to navigate MLMT courses three times over one year. The study enrolled 60 subjects ages four and older; 26 normal-sighted subjects and 28 visually impaired subjects, most commonly with a diagnosis of LCA or RP, completed the one-year study. At each visit, subjects completed testing using each eye, and then both eyes, at up to nine standardized, luminance levels (ranging from 1 to 400 lux). Course configuration was altered after each run according to a pre-determined randomization scheme, with each of 12 different courses (shown in Appendix 12.3, with one example in Figure 20) covering the same total distance with the same number of turns and obstacles.

The MLMT was carried out as described above in Section 5.1. Subjects were evaluated for accuracy and speed, and the MLMT results were compared with VA and VF tests, and a visual function questionnaire collected at the same visits (Chung et al. 2017).

5.4.2 Validation Study Results

5.4.2.1 Subject Disposition and Demography

Sixty subjects (29 normal-sighted and 31 visually impaired), ages four to 40, were eligible for participation. Twenty-eight visually impaired subjects and 26 normal-sighted controls completed all four visits, including one screening visit, two closely spaced visits at baseline (typically within four weeks of each other), and a final visit one year after baseline. Of the visually impaired subjects, 20 were diagnosed with LCA, five with choroideremia (CHM), four with RP, and one each with Stargardt disease and Usher syndrome.

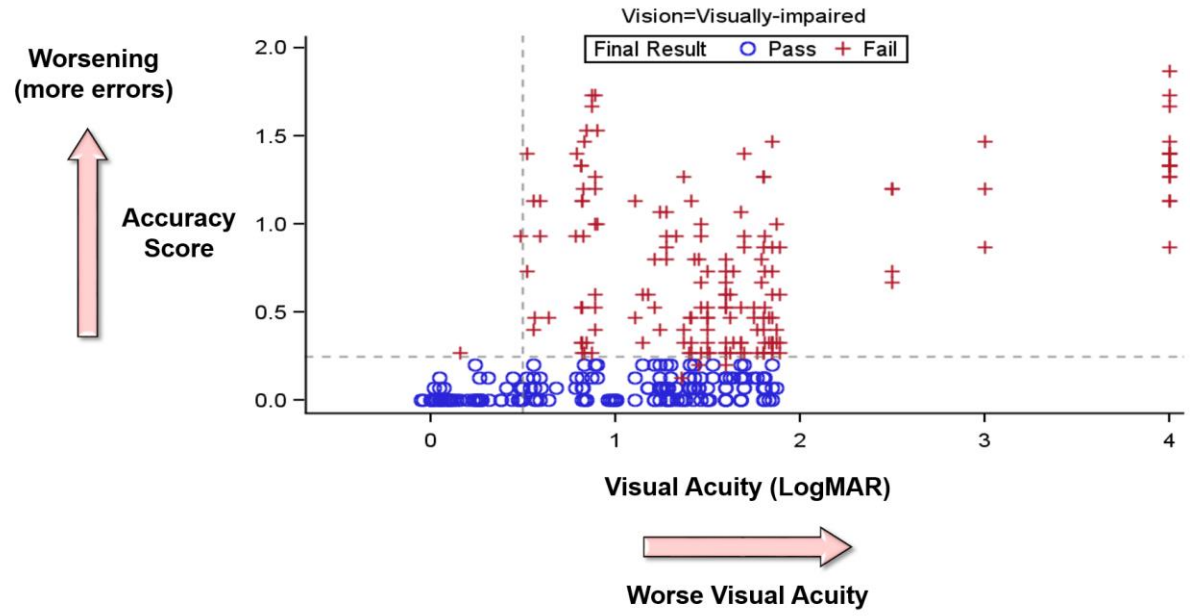
5.4.2.2 Results

The results of this study indicated that the standardized MLMT showed both construct and content validity. The MLMT showed construct validity by distinguishing between normal-sighted and visually impaired subjects. Normal subjects passed on both time and accuracy at all light levels, while visually impaired subjects demonstrated a wide range of failing and passing performances depending on levels of illumination for some conditions. Accuracy was measured using the accuracy score metric, more intuitively described as an error score, which divides the number of accuracy penalties by the total number of obstacles.

Content validity was supported by the VA and VF results. In normal-sighted subjects, VA and accuracy were both tightly clustered, while visually impaired subjects had more errors and more variable results with greater (worse) VA. Visually impaired subjects with VA of 0.5 LogMAR units (20/63 Snellen equivalent) or better had accuracy scores of zero (i.e., no errors) or close to zero, similar to normal-sighted subjects. Conversely, all visually impaired subjects with VA greater than 0.5 LogMAR units showed a range of accuracy performance, and those with greater than two LogMAR units had very high (poor performance) accuracy scores (Figure 22). A similar cut-off effect was observed for time. Overall, the correlation of average accuracy score

with mean VA was strong among visually impaired subjects, ranging from 0.75 to 0.86 across all visits and eyes.

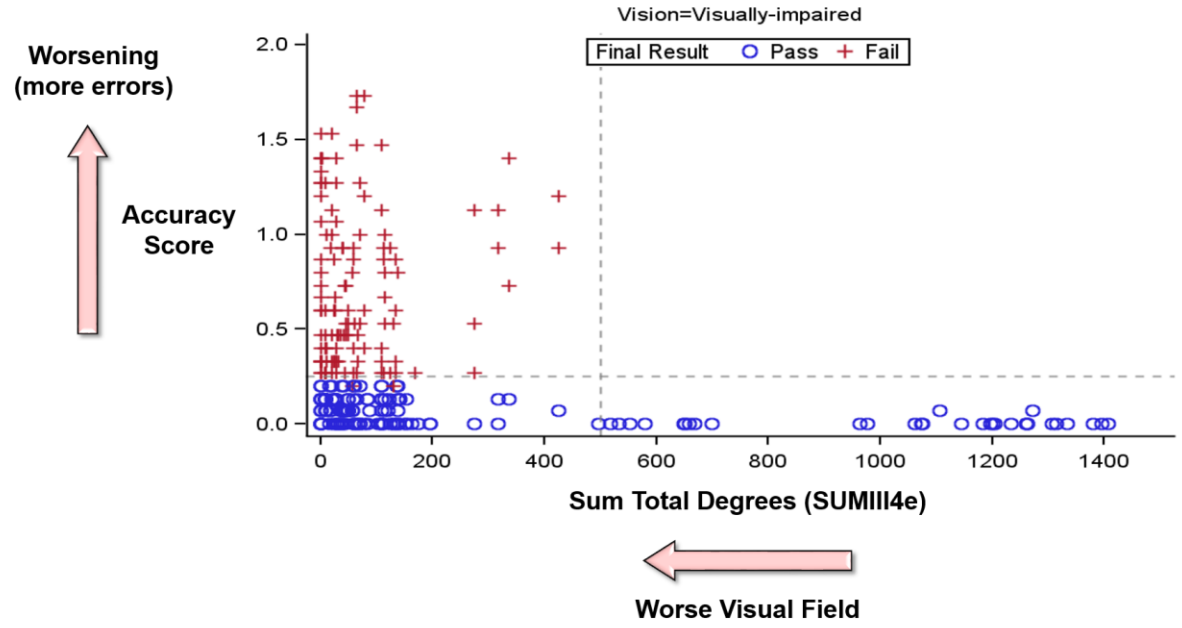
Figure 22: Visual Acuity and MLMT Accuracy Score, by Pass/Fail Status



The figure above includes multiple accuracy scores, at all light levels tested, for visually-impaired individuals. LogMAR 0 = 20/20 visual acuity. LogMAR 1 = 20/200 visual acuity.
Chung et al. (2017)

Among visually impaired subjects, correlations between mean accuracy score and sum total degrees on Goldmann VF testing (V4e and III4e test stimuli; see Section 6.4 for details) for each eye/visit combination ranged from -0.37 to -0.53, indicating only a weak to moderate correlation (Figure 23). Although the correlations did not indicate a strong *linear* relationship, a cut-off phenomenon was seen using the III4e data at 500 sum total degrees, below which the accuracy scores deteriorated (i.e., performance was worse for those with VF sum total degrees <500). Similar cutoffs were seen for the V4e data and with Humphrey VFs (foveal sensitivity and macula threshold).

Figure 23: Goldmann Visual Fields (III4e) and Accuracy Score on MLMT, by Pass/Fail Status



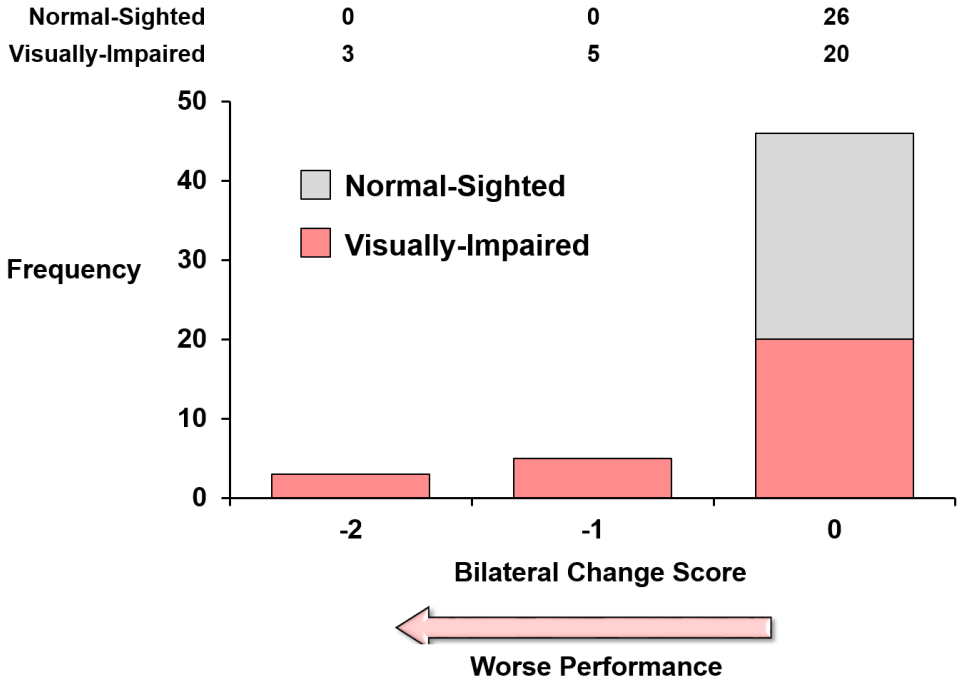
The figure above includes multiple accuracy scores, at all light levels tested, for visually-impaired individuals. Chung et al. (2017)

Normal-sighted subjects had consistently high scores on the visual function questionnaire, while visually impaired subjects showed a range of performance, reflected in the range of MLMT time and accuracy scores.

Finally, concordance of pass/fail scores between the two baseline visits (typically spaced 4 weeks apart) was used to assess test reliability. For the bilateral accuracy scores in the visually impaired subjects, using the lowest common lux level (defined as the lowest light level tested at both Baseline visits), the correlation between the two baseline visits was 94%. Using the highest common lux level (defined similarly), the correlations for accuracy scores between the two baseline visits was 98% (Chung et al. 2017).

Year 1 mobility test score changes were calculated for 54 subjects. All 26 normal-sighted subjects with Year 1 data had an MLMT score change of 0, reflecting no change. Of the 28 visually impaired subjects with Year 1 data, 20 (71%) had an MLMT score change of zero. The remaining eight visually impaired subjects had an MLMT score change of -1 or -2 (i.e., a worsening or needing a higher light level to pass). All of these subjects carried a diagnosis of LCA or RP, as opposed to CHM, Stargardt, or Usher. Among the 28 subjects with visual impairment, the negative MLMT score changes reflected an average decrease of approximately one-half of a specified light level/year. Thus, the test is sensitive to the progressive changes that occur in IRD.

Figure 24: Distribution of Score Changes using Bilateral Assessments at 1 Year



Chung et al. (2017)

5.4.2.3 Conclusions

Overall, the standardized mobility test showed both construct and content validity in differentiating low vision from control populations and identifying a range of performance in low vision subjects. The test successfully differentiated among those with clinical diagnoses of IRDs, as all eight subjects whose MLMT score change declined over the course of one year had a diagnosis of LCA or RP, consistent with the progression of the disease with respect to functional vision.

Course assessment has shown that all twelve courses were of equal difficulty (Chung et al. 2017). Visually impaired subjects demonstrated high test-retest reproducibility, with a high concordance for the pass/fail outcome and high correlation for accuracy score and time components between the two baseline visits. Quality assurance grading activities showed high reproducibility of results and reliability of this endpoint (Chung et al. 2017). The MLMT exhibited a clear relationship to VA and VF, specifically a threshold effect such that performance on the MLMT declined markedly when VA and VF fell below certain thresholds. Note that this helps to establish the validity of the MLMT, since it shows that performance on the test (MLMT) is affected by VA and VF. In other words, this measure of functional vision, which can be considered the performance output of visual function, reflects the status of VA and VF, measures of visual function.

Considering the context of the clinical deficit specific to this disease and the need for a clinically meaningful endpoint to measure the subject's functional vision, the MLMT was developed as a

novel endpoint. Mobility testing in the earlier Phase 1 studies supports the feasibility of using this visually dependent task as an outcome measure, and the Mobility Test Validation Study established the content and construct validity of this test. This endpoint was then utilized in Study 301.

6 MEASUREMENTS OF VISUAL FUNCTION

A full description of the visual tests used in the voretigene neparvovec development plan is in Appendix 12.2.

6.1 Visual Function vs Functional Vision

Visual function can be described as how the *eyes* function (individually or together), which in turn can provide an estimate of functional vision. Functional vision can be described as how a *person* functions or performs in a vision-related activity such as mobility and navigation, and visual communication and visual occupational abilities. Changes in functional vision can be assessed by objective performance of a controlled task requiring vision, and scored based upon timing and error rate.

6.2 Full-field Light Sensitivity Threshold Testing

Full-field light sensitivity threshold testing assesses light sensitivity of the entire retina by measuring the subject's perception of different luminance levels (i.e., differing levels of light brightness). Full-field light sensitivity threshold testing is a subjective physiological test of retinal function relevant to the visual deficit experienced by patients with IRDs. To perform FST testing, the subject's eyes are dilated and then double patched in a dark room for 40 minutes for dark adaptation. After this, each eye is tested individually, keeping the contralateral eye patched. The subject's chin is placed on a chin rest in front of a Ganzfeld dome (a 40 cm diameter dome-shaped white screen). When testing commences, a light flashes inside the entire dome accompanied by a beeping sound. Each time a beep sounds, subjects must indicate whether or not they saw a light by pressing a "yes" or "no" button. Light flashes continue at different intensities and an algorithm identifies the minimum luminance (brightness) at which the subject reliably perceives light. In the Phase 3 study, subjects were tested using white, red, and blue light stimuli for each eye separately.

Unlike many other tests of visual function, FST testing is not affected by nystagmus. Additionally, FST testing has an extensive dynamic range, which allows it to be used to evaluate both individuals with normal vision or lesser degrees of impairment, and those individuals with more profound visual disability. In addition, this test measures overall visual function of the eye being tested and does not incorporate the sampling bias inherent in tests that evaluate specific areas of retina/vision and then extrapolate the findings to overall visual function.

Full-Field Light Sensitivity Threshold testing is a relevant measure to assess the recognized visual disability known as nyctalopia, or night blindness, experienced by patients with *RPE65* mutation-associated retinal dystrophy. Full-Field Light Sensitivity Threshold testing measures the threshold, or limits, of light brightness that can be seen, to determine the sensitivity of the visual system; threshold is the reciprocal of sensitivity (i.e., low threshold equals high sensitivity). Changes in light sensitivity reflective of photoreceptor function can be tracked over time. Results are measured in relative units (decibels or dB), which are converted to absolute units (candela second per square meter or $cd.s/m^2$) to allow comparison across sites and subjects. The metric for analysis uses $\log10(cd.s/m^2)$. For $\log10(cd.s/m^2)$, a more negative result equals a lower threshold and thus improved light sensitivity, indicating improved photoreceptor function. This endpoint evaluates the ability of subjects to detect light as mediated by the photoreceptors

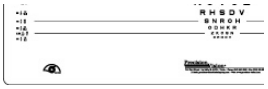
affected in IRD associated with biallelic *RPE65* mutations; significant improvement in light sensitivity demonstrates that the visual pathway of associated photoreceptors is favorably impacted.

6.3 Visual Acuity

Visual acuity is a traditional measure of central visual function, particularly the ability of the eye to perceive details. Primarily cone-mediated, visual acuity is the most common measure of visual function both in clinical practice as well as in clinical trials. Loss of acuity manifests as a decrease in the ability to perform detail-oriented tasks, such as reading and face recognition. In the patient population with IRD due to biallelic RPE65 mutations, VA is often severely impaired early in life.

In the voretigene neparvovec clinical program, VA testing used high contrast charts with standardized letters of graded sizes to determine the smallest object seen at a specified distance. Early Treatment of Diabetic Retinopathy Study (ETDRS) VA test charts (Figure 25), the gold standard for VA measurements in clinical studies, were used for most subjects in the clinical studies. For some young children, an analogous HOTV chart was used. HOTV charts include only the letters H, O, T and V, all of which center around a vertical axis and can be identified verbally by young children or shown to the test-taker on a matching HOTV card.

Figure 25: Example of ETDRS Visual Acuity Test Chart



Subjects were tested (using best correction [with optimal glasses/contact lens prescription] and well-illuminated charts) with each eye individually at three distances: 4 meters, 2 meters, and 0.5 meter. Visual acuity was determined based on the lowest lines (smallest letters) on which letters were correctly identified at each distance. The ETDRS chart includes letter sizes on each line following a geometric progression, such that VA can be converted to a visual angle score (LogMAR, or **Log**arithm of the **M**inimum **A**ngle of **R**esolution) allowing for comparison analyses, where *smaller* LogMAR values indicate *better* acuity (i.e., less VA loss). For the VA analyses, a 0.1 change in LogMAR corresponds to a 5-letter (equivalent to one line) change on the ETDRS chart.

For subjects unable to correctly identify the largest line of letters on the chart, off chart VA measurements were collected (i.e., counting fingers, hand motion perception, light perception, no

light perception) and then were assigned a LogMAR value using the scale adapted from Holladay (2004). This scale utilizes a 1-log-unit step between, for example, counting fingers and hand motion perception. Given this large step, this scale is conservative with respect to quantifying VA in assessment of safety, as it assigns worse (higher) acuity to off-chart VA than other scales. In response to recommendations from regulators and the Data Safety Monitoring Board overseeing the clinical program, a scale with a reduced 0.3-log-unit step between counting fingers and hand motion was used for sensitivity analyses beginning in 2013. This scale, adapted from Lange et al. (2009), was recommended given concerns with overestimating any treatment effect (improvement or reduction in LogMAR) for subjects with off-chart vision measurements at Baseline; this same scale is associated with Freiburg vision testing, or FrACT, though this testing method itself (developed by Professor Michael Bach [senior author on the Lange et al. (2009) publication] and colleagues for patients with very low vision) was not used in the clinical program.

6.4 Visual Field

Visual field refers to the area in which objects can be detected in the periphery of the visual environment, while the eye is focused on a central point. Loss in visual field (i.e., decreased peripheral vision or increased "tunnel vision"), manifests in an inability to detect peripheral objects and, often, in a reduced ability to avoid obstacles. Both visual acuity and visual field impact the performance of activities of daily living.

Visual fields can be measured by using kinetic and/or static techniques with instruments that are operated either manually or automatically (computerized). All methods include an apparatus where patients are seated with their chin in a chin rest, looking at a dome-shaped screen, and asked to focus the eye being tested on a central point while the contralateral eye is patched. Kinetic perimetry involves moving the test object (i.e., light stimulus) from the non-seeing (i.e., far periphery) to the seeing area (with the size and brightness of the test stimulus held constant) and mapping the boundary where the test stimulus is first detected. Threshold static automated perimetry measures the relative intensity thresholds (levels of brightness) of individual points in the visual field; the size and location of the target is kept constant and the brightness is varied until a threshold level is identified for each test location. In the Phase 3 clinical trial, kinetic fields were measured with manual Goldmann perimetry (assessing the full extent of the visual field for each eye) and static fields were measured using Humphrey computerized testing (evaluating the sensitivity of specific points in the central retina [macula and fovea]).

Each test has benefits and drawbacks. Goldmann VF testing is frequently used in low vision patients and those with nystagmus since the technician (perimetrist) conducting the test can monitor patient fixation. Additionally, Goldmann perimetry is better at identifying islands of visual field and/or scotomas (isolated areas of inability to see) in the periphery. Computerized visual fields such as Humphrey, on the other hand, are beneficial because they are automated and based on computerized algorithms. The results are presented quantitatively and can be monitored over time as the algorithm automatically compares each subject's result to age-matched normative data. The Humphrey analyzer is also more sensitive to slight changes in the central field (field corresponding to the macula and fovea).

Goldmann VFs were reported as sum total degrees that the subject was able to perceive across all 24 meridians. The extent of VF was measured along each of the 24 meridians from the central fixation point to the boundary (i.e., point of the isopter intersection) of the detected visual field; a summation of the measure from each of the 24 meridian measurements represents the sum total degrees for that eye. Higher sum total degrees indicate a greater area of functional and light sensitive retina, corresponding to a greater field of vision for the tested eye. Using this approach, the maximal visual field is approximately 1200 to1400 sum total degrees in individuals without visual impairment. In clinical practice, Goldmann VFs are usually assessed qualitatively, with a subjective evaluation of changes in shape, size, and area of the fields over time. The use of sum total degrees allows for a quantitative assessment and provides a numeric estimate of the entire field, which can be analyzed over time.

6.5 Endpoint Selection for Phase 3 Study

Key outcomes from the June 2011 Advisory Committee meeting (convened to discuss cellular and gene therapy trials for the treatment of retinal disorders) included recognition of the need for novel endpoints tailored to disease and clinical deficit and the recommendation for the use of multiple tools to measure visual function and functional vision, as well as consideration of patient reported outcomes related to activities of daily living. These recommendations, in addition to inputs from multiple discussions and meetings with the FDA, were incorporated into the design of the voretigene neparvovec development program.

For the Phase 3 study, Spark Therapeutics sought a measure of *functional vision* as the primary endpoint, since measures of functional vision are the most straightforward to relate to clinically meaningful changes for patients. Assessments of functional vision can be either laboratory-based or "real-world" based. Since Spark Therapeutics sought to develop quantitative measures of change in functional vision, a laboratory-based method was selected. A challenge in the setting of this rod-mediated disease was the dearth of well-studied endpoints that integrate into the testing rubric a range of levels of illumination, and since nyctalopia is a hallmark of this disease, it was critical to develop a test that incorporated levels of illumination as a controlled and quantifiable aspect of the test. Successful navigation of the MLMT course integrates input from visual acuity, visual field, and light sensitivity, all of which are functions specifically affected in IRD associated with biallelic *RPE65* mutations. Visual fields (both static and kinetic) were also assessed separately in this trial. Thus, the MLMT, a measure of functional vision, was selected as the primary endpoint, with additional measures of visual function included as secondary and exploratory endpoints.

In addition to the primary endpoint, Spark Therapeutics chose three secondary endpoints, two of which are measures of visual function. The first of these, FST, is well-suited for a rod-mediated disease, and can be used even in the setting of nystagmus. Since the mechanism of action of voretigene neparvovec is the restoration of the visual cycle and thus improved sensitivity to light, this seemed a straightforward choice. The second secondary endpoint was MLMT on the first eye. The original proposal had been to combine all three eye-patching conditions – right eye alone, left eye alone, and bilateral testing – to achieve a sum score for MLMT. However, further deliberations led to the decision to only use the bilateral testing condition as the primary endpoint, since this is the most relevant clinically. Subsequently, a concern was raised that use of the bilateral testing condition only might serve to mask poor performance of the investigational

agent, since the bilateral testing condition will reflect the performance of the better eye. For this reason, performance on the MLMT using the first eye was added as a secondary endpoint. Visual acuity was the third secondary endpoint. Given that this is a rod-mediated disease, it would not necessarily be expected that VA would improve; this endpoint was included as the third secondary endpoint based on VA observations in the small Phase 1 study.

To further characterize functional vision, a visual function questionnaire and community-based functional vision assessments (also referred to as Orientation and Mobility or "O&M" assessments) were included as additional measures to provide more complete insight into aspects of functional vision and individualized real-world performance. Additional visual function tests utilized in this clinical program evaluated function of both the central (*e.g.*, HVF, VA) and peripheral retina (*e.g.*, GVF, FST) under a range of testing conditions, providing information on both rod and cone photoreceptor function. Exploratory endpoints of contrast sensitivity and pupillometry were included in the trial but were non-informative and are not discussed in this briefing document.

The overarching goal of selecting and optimizing the efficacy endpoints during the voretigene neparvovec clinical development program was to capture subjects' visual function and functional vision in a quantifiable manner, over a wide range of parameters, in order to have a comprehensive assessment of both subjects' clinical presentation (range of functioning or vision loss) and treatment response following administration. The combination of a novel functional vision endpoint along with more conventional measures of visual function meets this goal and provides a robust evaluation of the effects of voretigene neparvovec in patients with *RPE-65* mutation associated IRD.

7 *RPE65* MUTATION-ASSOCIATED RETINAL DYSTROPHY NATURAL HISTORY STUDY

There are limited historical data characterizing the natural progression of *RPE65* mutation-associated retinal dystrophy. In addition to being a rare disease, the mutation was only recently identified, and molecular genetic testing is relatively new and not yet used universally. Further, much of the data that are available are confounded by the use of multiple clinical diagnoses that may have been inconsistently assigned to similar clinical presentations. Therefore, Spark Therapeutics conducted a retrospective chart review (the Natural History Study) of patients with confirmed biallelic *RPE65* mutations to better understand the clinical course of this condition. The Natural History Study included 70 patients from seven internationally recognized tertiary referral centers and utilized ocular history review and results from clinical testing, including VA, VF, and OCT. In addition, electroretinography, color vision, and comprehensive ophthalmic examination data were also collected, when available.

7.1 Methodology

The Natural History Study was a cross-sectional analysis of longitudinal data (i.e., from at least two visits for a given subject) from the charts of patients with confirmed biallelic *RPE65* mutations. Data were retrieved from the charts of all subjects who met eligibility criteria at the seven referral centers, which included 70 male and female patients born between January 1, 1963 and December 31, 2010. Ocular history and visual function testing data were abstracted from the collected charts and analyzed.

The primary parameters analyzed included VA, Goldmann kinetic VF, and OCT. Additional demographic and visual parameters were collected, including ERG, color vision, ophthalmic examinations, ocular history, clinical diagnoses, and genotype when available.

The data were collected and summarized using descriptive measures. Since longitudinal data were not available on all subjects for all testing parameters, and the duration of follow-up varied, these primary assessments were analyzed as a function of age as a proxy for time, so that all individual data points could be included in the analysis.

Cross-sectional analyses were conducted to examine the effect of age on VA, Goldmann kinetic VF by test stimulus type, and OCT findings. Mixed-effects linear/polynomial regression models were applied separately to VA, VF, and OCT to determine whether age had an association with any of these parameters. This approach accounts for correlations arising from the repeated measures and uses all measurements obtained from each subject.

7.2 Sources

Data were taken from seven referral centers located in Belgium (Ghent), Germany (Giessen), Massachusetts US (Boston), Denmark (Copenhagen), Oregon US (Portland), Brazil (Sao Paulo), and France (Montpellier). The study included participants with confirmed biallelic *RPE65* mutations. A total of 70 patients met the inclusion/exclusion criteria (see Appendix 12.4) and were included in the study.

7.3 Demographics

A summary of demographic characteristics is shown in Table 14. The average age at first visit in the charts of subjects was 15 years, with a range of one to 43 years. The study population was 60% female, 67% white, and predominantly non-Hispanic or Latino (83%). All eligible subject charts had confirmation of autosomal recessive *RPE65* mutations.

Table 14: Summary of Demographics in the Natural History Study

Parameter/Category/Statistic	Eligible (N = 70)	Ineligible (N = 32)	Total (N = 102)
Age (Year)*			
Mean (SD)	15 (11.8)	15 (18.3)	15 (14.9)
Median (IQR)	9 (3,18)	9 (3, 35.5)	9 (3, 24)
Min, Max	1, 43	1, 61	1, 61
Gender, n (%)			
Female	42 (60.0)	21 (65.6)	63 (61.8)
Male	28 (40.0)	11 (34.4)	39 (38.2)
Race, n (%)			
White	47 (67.1)	23 (71.9)	70 (68.6)
Asian	2 (2.9)	1 (3.1)	3 (2.9)
Black or African American	14 (20.0)	3 (9.4)	17 (16.7)
Other	1 (1.4)	2 (6.3)	3 (2.9)
Unknown	6 (8.6)	3 (9.4)	9 (8.8)
Ethnicity, n (%)			
Not Hispanic or Latino	58 (82.9)	22 (68.8)	80 (78.4)
Hispanic or Latino	9 (12.9)	6 (18.8)	15 (14.7)
Unknown	3 (4.3)	4 (12.5)	7 (6.9)

*Age is approximate since only birth years are available.

7.4 Diagnosis

More than 20 distinct clinical diagnoses were reported in the charts of the 70 subjects with confirmed biallelic *RPE65* mutations, with some subjects having more than one diagnosis at the time of the initial visit in the chart. In addition, subjects may have received one clinical diagnosis early on, which was subsequently changed over time as more information (usually genetic testing results) became available. Among the clinical diagnoses at the time of the first reported visit, 42 (55.3%) were LCA, six (7.9%) were RP, five (6.6%) were tapetal retinal dystrophy, 5 (6.6%) were Severe Early Childhood Onset Retinal Dystrophy (SECORD), and four (5.3%) were Early Onset Severe Retinal Dystrophy (EOSRD).

The age at clinical diagnosis was obtained from the 70 subject charts. Sixty-seven (95.7%) subjects were 18 years of age or younger at the time of the first recorded clinical diagnosis or the onset of symptoms noted in the ocular history.

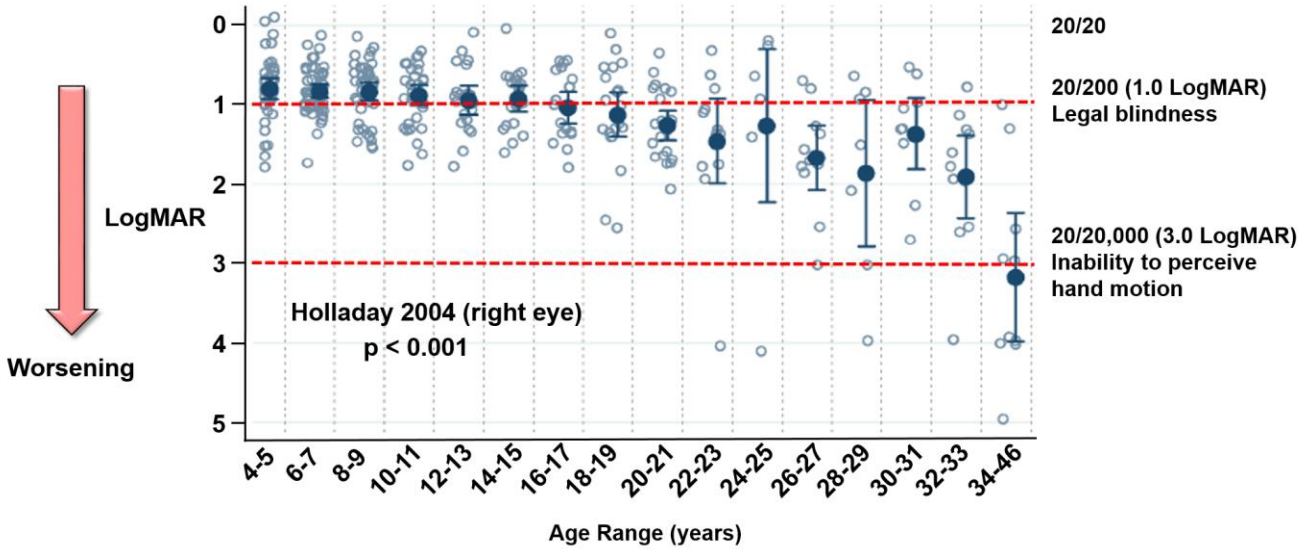
7.5 Results

Visual Acuity

In the Natural History Study, each subject had a varying number of measurements (1 to 41); multiple measurements for an eye on the same date were averaged. Visual acuity was modeled separately for each eye using a mixed-effects polynomial regression model. The modeled quadratic trends of age on VA were statistically significant ($p<0.0001$) for each eye, consistent with the pattern of observed means appearing in Figure 26 below. There was individual variability in VA, however, VA appears worse in older subjects. While some individuals had normal or near-normal VA at young ages, the data in Figure 26 show that VA, on average, was markedly impaired and fairly stable in this cohort during the first decade of life. The mean VA for all patients (all VA test results across all age groupings) falls into the "low vision" category (0.6 LogMAR, equivalent to 20/80) (Colenbrander 2002).

Around the age of 16, there is a change in the mean LogMAR, where it begins to exceed 1.0 LogMAR (equivalent to 20/200, the threshold for "legally blind"). By the age of 18, more than half of this cohort were legally blind, as defined by VA of 1.0 LogMAR or worse in the better eye. Visual acuity loss was more significant in older patients; the mean LogMAR exceeded 2.0 (equivalent to 20/2000) in the oldest patient grouping (34-46 years).

Figure 26: Natural History Study - Visual Acuity by Age



Bars represent mean and 95% confidence interval for each age grouping. Dots represent actual values.

Visual Field

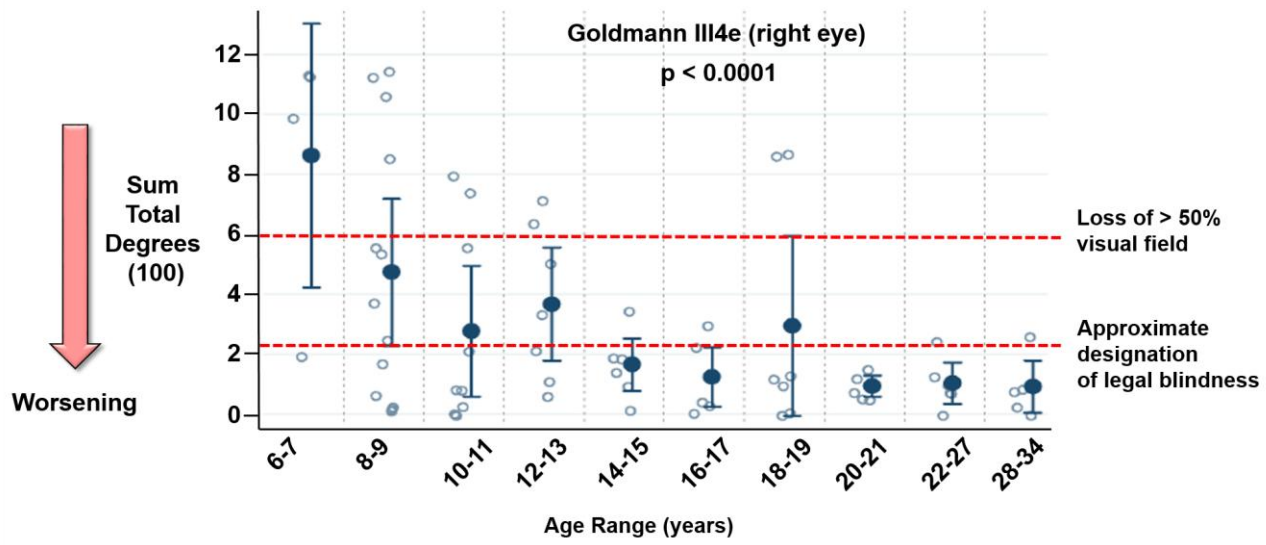
Visual field information was collected primarily from Goldmann kinetic perimetry, using sum total degrees as the unit of measure (see Section 6.4 for details).

Subjects also had VF data with a varying number of repeated III4e and V4e measurements. Similar to VA, multiple measurements obtained for the same eye and same test stimulus type on the same date were averaged. To determine the association of age on visual field, mixed effects linear regression models used sum total degrees as the outcome and linear age, random intercept, and age by test stimulus type (III4e vs. V4e) interaction. As with VA, in the two separate left and

right eye models, the marginal effects of age were significant for III4e ($p<0.0001$) and for V4e ($p<0.0001$).

Declining VF was associated with advancing age, starting as early as the first and second decades of life.

Figure 27: Natural History Study - Visual Field by Age



Bars represent mean and 95% confidence interval for each age grouping. Dots represent actual values.

The Natural History Study cohort had approximately 50% or less of the total possible field, even in the younger age categories in which fields were evaluated. In general, compromise in VF preceded decline in VA. The ICO suggests that 50% of normal VF constitutes moderate impairment (Colenbrander 2002), while the AMA Guidelines (2008) classify 30-49% impairment of the field as moderate vision loss and 50-69% as severe vision loss.

Other Measures

On optical coherence tomography, no statistically significant age effect on retinal or outer nuclear layer thickness was observed for either eye, although the analyses are limited by the small number of subjects (32) and longitudinal data points, making it difficult to draw any conclusions. The prevalence of abnormalities in ERGs, color vision, and other ophthalmologic findings within the study population was generally consistent with the known clinical presentation. The presence of structural abnormalities on ophthalmologic exam (lens, macula, optic disc, vessels, periphery) generally was greater with age, and the findings were consistent with progressive retinal degeneration.

Summary

Overall, the results of Natural History Study illustrate the serious and significant vision loss due to biallelic *RPE65* mutation-associated retinal dystrophy. The findings from the Natural History Study were complementary to existing literature describing individuals with biallelic *RPE65* gene mutations, but represent the largest number of subjects reported to date in a single study.

The retrospective nature of this study has limitations, primarily the lack of standardization of data collection and the evolution of imaging technology. However, the design is appropriate for this patient population, given its rarity and the rate of progression of the disease. The number and variety of clinical diagnoses, as well as the number of unique genetic mutations reported for the subjects of whose charts were included in this study demonstrate a high degree of heterogeneity and the lack of a consistent genotype-phenotype correlation, underscoring the need for genetic testing. Even with this heterogeneity, findings from this study suggest age-related decline in VA and VF in individuals with confirmed *RPE65* mutations, with no evidence of spontaneous sustained improvement in any individual for either of these parameters. While variability in visual assessment parameters exists and the optimal therapeutic window is not known, findings from this study support the contention that therapeutic intervention has the potential to alter the progressive natural history of the disease.

8 EFFICACY IN THE PHASE 1 AND PHASE 3 STUDIES

Summary

- Voretigene neparvovec treatment resulted in clinically meaningful and statistically significant improvements in functional vision, light sensitivity, and visual function compared to control subjects, with observed improvement as early as 30 days after administration.
- Phase 1 studies showed consistent and durable improvements in light sensitivity after treatment with voretigene neparvovec; the majority of subjects demonstrated improvements in visual function and functional vision for at least four years.
- The pivotal Phase 3 Study 301 met its pre-specified primary endpoint, demonstrating significant improvement in functional vision at lower light levels, as measured on the MLMT.
- Subjects in Study 301 also showed an improvement on secondary endpoints including FST and monocular MLMT; VA was not significantly different between groups. Improvements were also observed on the exploratory VF endpoints.
- The visual function questionnaire and community-based functional vision assessments suggest improvements in performing daily activities after treatment with voretigene neparvovec.
- Findings from the Phase 3 Control subjects treated with voretigene neparvovec after the initial 1 year of observation replicated the overall benefit and improved functional vision and visual function observed in the Original Intervention subjects.
- Improvement after voretigene neparvovec was maintained throughout the efficacy follow-up period, up to three years in Phase 3, with observation ongoing.

8.1 Phase 1 Studies 101 and 102

Studies 101 and 102 were Phase 1 studies designed to assess the safety, tolerability, and efficacy of subretinal administration of voretigene neparvovec.

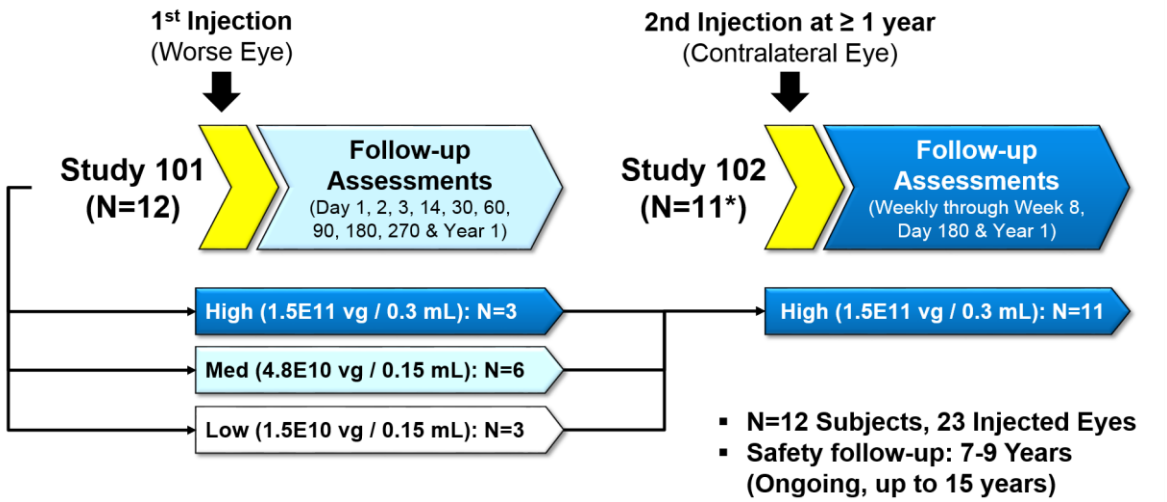
8.1.1 Clinical Design

Study 101 was a first-in-human, open-label, dose escalation study in 12 subjects with IRD due to confirmed autosomal recessive RPE65 gene mutations who received a single unilateral injection of voretigene into the worse-seeing eye at one of three doses:

- a low dose of 1.5E10 vg (n = 3)
- a medium dose of 4.8E10 vg (n = 6)
- a high dose of 1.5E11 vg (n = 3)

Follow-up assessments for Study 101 were performed at multiple timepoints throughout the first year after administration, at Year 1.5, and annually thereafter. After the first year, subjects had the option of enrolling in Study 102, which was an open-label follow-on to Study 101, in which 11 of the 12 subjects received 1.5E11 vg in a total subretinal volume of 0.3 mL (the high dose in Study 101) in the previously uninjected, contralateral eye.

Figure 28: Clinical Study Design of Study 101 and 102



*one subject did not meet eligibility criteria for contralateral eye due to glaucoma

Adults and children at least eight years of age, diagnosed with *RPE-65* mutation-associated retinal dystrophy, were recruited into Study 101. Subjects were required to have a molecular diagnosis of *RPE65* mutations (homozygotes or compound heterozygotes). Subjects were required to have a VA of 20/160 or worse, or have a VF of less than 20 degrees in any of 24 meridians in the eye to be injected. Subjects also had to have sufficient viable retinal cells as determined by non-invasive means, such as OCT and/or ophthalmoscopy.

In Study 102, subjects had to have completed at least one year of follow-up in Study 101. Additionally, subjects had to have VA greater than or equal to light perception, and sufficient viable retinal cells in the contralateral, previously uninjected eye.

The Phase 1 studies were designed primarily to assess safety. A number of different efficacy outcome measures were explored in both studies and focused on the change in visual function as measured by subjective, psychophysical tests and by objective, physiologic tests. Measures to assess efficacy in Phase 1 included VA, FST, VF, and an early version of the mobility test (see Section 6 for details on assessments). Efficacy was determined by comparing the pre-injection visual function measurements with those measured following administration of voretigene neparvovec for each individual subject. In Study 101, efficacy was also assessed by comparisons to the uninjected eye.

8.1.2 Study Population

8.1.2.1 Demographics

Demographic data for Study 101 are summarized in Table 15, overall and by dose. The study population in Study 102 consisted of 11 of the 12 individuals who participated in Study 101.

Table 15: Summary of Demographics in Study 101

Parameter	Category/Statistic	Low Dose (N = 3)	Middle Dose (N = 6)	High Dose (N = 3)	Total (N = 12)
Gender, n (%)	Male	1 (33%)	4 (67%)	2 (67%)	7 (58%)
	Female	2 (67%)	2 (33%)	1 (33%)	5 (42%)
Race, n (%)	White	3 (100%)	5 (83%)	3 (100%)	11 (92%)
	Asian	0	1 (17%)	0	1 (8%)
Ethnicity, n (%)	Not Hispanic or Latino	3 (100%)	6 (100%)	3 (100%)	12 (100%)
	Hispanic or Latino	0	0	0	0
Age, years	Mean (SD)	23.7 (4.0)	14.7 (6.6)	30.3 (17.2)	20.8 (11.2)
	Median (IQR)	26.0 (7.0)	13.5 (11.0)	36.0 (33.0)	19.5 (15.5)
	Min, Max	(19, 26)	(8, 24)	(11, 44)	(8, 44)

8.1.3 Efficacy Results

In Study 101, 12 subjects were enrolled (Table 16). One subject who participated in Study 101 was not eligible for Study 102 due to glaucoma in his uninjected eye. No subjects withdrew from either study.

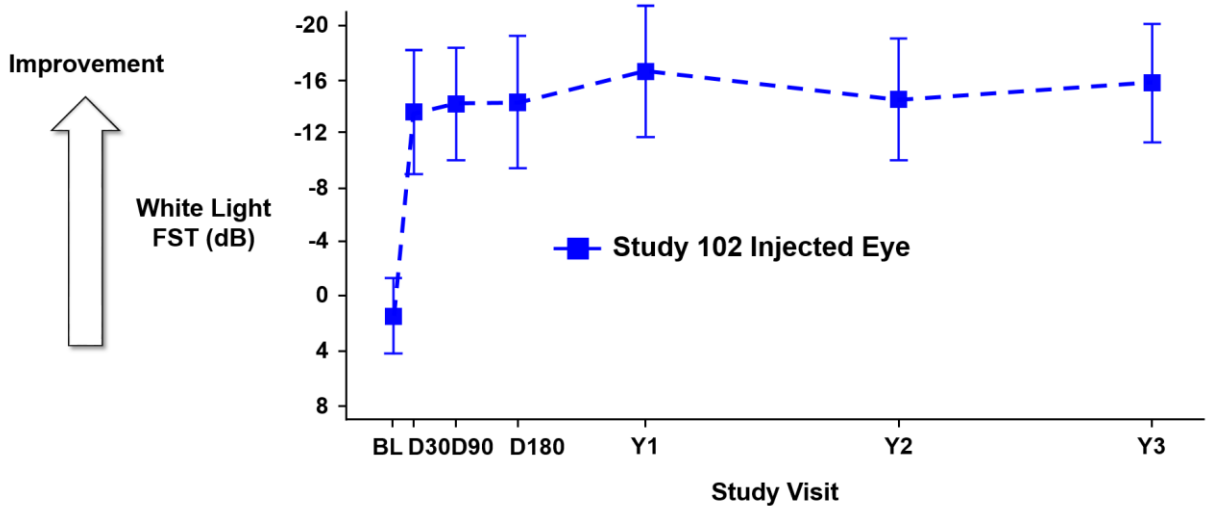
Table 16: Subject Disposition in Study 101

	Low Dose (N = 3)	Middle Dose (N = 6)	High Dose (N = 3)	Total (N = 12)
Enrolled	3 (100%)	6 (100%)	3 (100%)	12 (100%)
Received study treatment	3 (100%)	6 (100%)	3 (100%)	12 (100%)
Completed	3 (100%)	6 (100%)	2 (67%)	11 (92%)
Ongoing	0	0	1* (33%)	1* (8%)
Discontinued	0	0	0	0

*At the time of the data cut-off for the Study 101 Clinical Study Report (14-Oct-2014), one subject was ongoing

Full-field light sensitivity threshold testing in Study 101 indicated that, the injected eye became more sensitive (i.e., responded at a lower light intensity) after voretigene neparvovec administration and remained so over the follow-up period in the majority of subjects. In Study 102, seven of the 11 subjects showed consistently increased light sensitivity in the injected eye (Figure 29). Given the mechanism of action for voretigene neparvovec, the functional improvement at lower light levels is clinically relevant to patients suffering from this disease, as its progression often leads to decreased light sensitivity and night blindness.

Figure 29: FST Testing Results in Phase 1 Studies

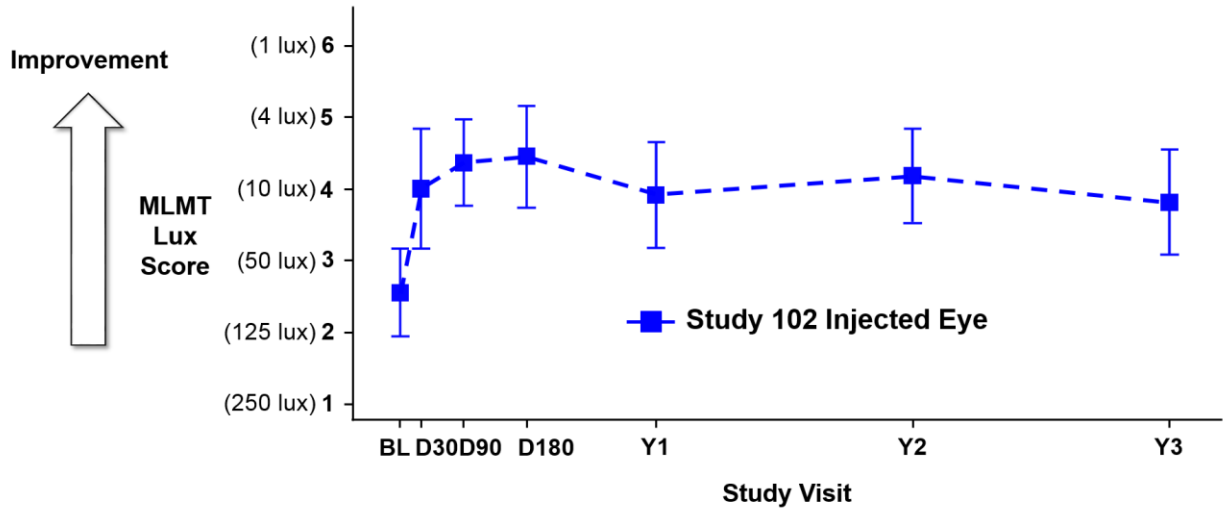


BL: Baseline; N = 11. Data presented as mean ± SE

Mobility testing evaluated subjects' ability to navigate accurately through a course and avoid obstacles under defined lighting conditions and within a specified time limit. During the course of Study 101, the mobility test was refined and standardized, which affected both the number of subjects considered evaluable and the interpretation of the results. However, approximately half of the evaluable subjects experienced some improvement in mobility testing.

In Study 102, mobility test results showed improvements in functional vision at lower light levels in eight of the 11 subjects (Figure 30).

Figure 30: Mobility Test – Change from Baseline to Year 1: Study 102



BL: Baseline; N = 11. Data presented as mean ± SE

At the time of BLA data cut-off (18-May-2016), 11 (100%) subjects had completed the Study 102 Year 3 study visit. Mobility test results continued to show improvements in functional vision at lower light levels. Full-Field Light Sensitivity Threshold test results also continued to show an overall improvement in light sensitivity compared to Baseline. Overall, the functional vision and visual function changes in the second eye suggest consistent, durable improvements in retinal sensitivity, as assessed by FST and mobility testing through at least three years.

8.2 Phase 3 Study 301

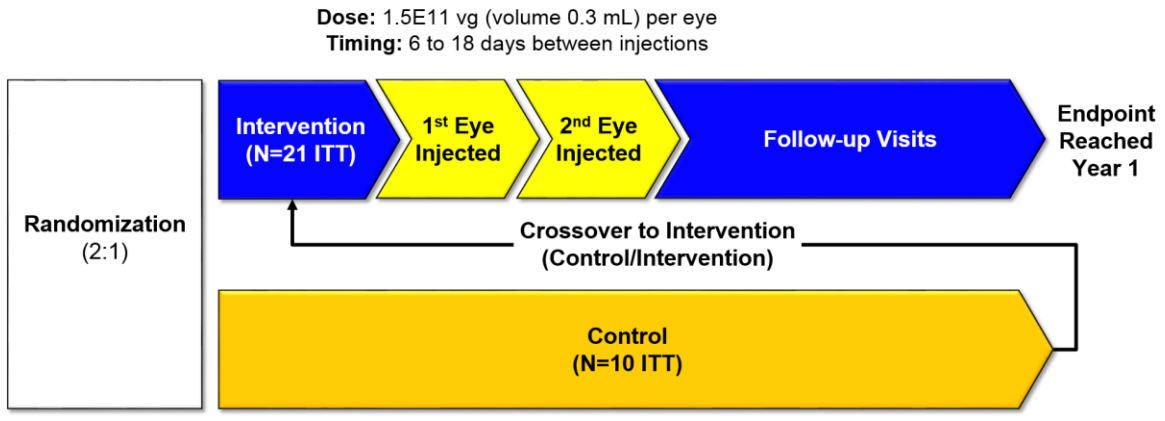
Study 301 was designed to assess the safety, tolerability, and efficacy of sequential, bilateral, subretinal administration of voretigene neparvovec in subjects with biallelic *RPE65* mutations.

8.2.1 Clinical Design

Study 301 was an open-label, randomized, controlled Phase 3 study in which patients with confirmed biallelic *RPE65* mutations were randomized 2:1 to Intervention (n=21) or Control (n=10). A CLIA-certified laboratory confirmed *RPE65* mutations if adequate records (from a CLIA-certified laboratory) were not available. The study was conducted at two sites: Children's Hospital of Philadelphia (CHOP) and the University of Iowa.

The design of Study 301 is shown in Figure 31. Subjects randomized to the Intervention group received near-simultaneous (no more than 18 days [12 days ± 6 days] apart), sequential injections of 1.5E11 vg voretigene neparvovec to each eye. Subjects randomized to the Control group did not receive voretigene neparvovec until one year after their Baseline evaluation. Since the trial included pediatric subjects, sham surgeries/injections were not performed in the Control group. Each dose of voretigene neparvovec was delivered in a total subretinal volume of 0.3 mL, and the procedure was conducted under general anesthesia. Details on the injection procedure can be found in Appendix 12.1. Subjects were treated with systemic corticosteroids for 18 to 30 days in the perioperative period to minimize inflammation associated with the surgical procedure and to reduce the potential for an immune response to the voretigene neparvovec capsid and transgene product.

Figure 31: Design of Study 301



mITT (Intervention, n=20; Control, n=9): 1 Control subject withdrew consent; personal reasons. 1 Intervention subject withdrawn by physician; surgical risk due to severe retinal thinning.

Subjects had a Screening Visit, Baseline Visit (60-90 days before voretigene neparvovec administration), and four visits (30 days, 90 days, 180 days, and one year after voretigene neparvovec administration) in which testing was conducted for the efficacy evaluations. Control subjects completed evaluations at the same timepoints, but did not receive any intervention during the year of observation. A full schedule of assessments can be found in Appendix 12.5.

Efficacy endpoints were compared between the Intervention and Control groups after one year. After the first year, subjects from the Control group were allowed to crossover and receive near-simultaneous (within 6-18 days), sequential injections of 1.5E11 vg voretigene neparvovec to each eye, provided they still met all study eligibility criteria. Additional annual visits are being conducted to evaluate subjects for a period of 15 years after receiving voretigene neparvovec to assess the long-term safety of the recombinant AAV vector and for continued evaluation of any therapeutic effects of the transgene.

For post injection analyses, "injection baseline" was defined as baseline. For the Original Intervention group, injection baseline is the same Baseline as the pivotal portion of Study 301. For the Control/Intervention group, the study collected updated baseline data for several assessments (vital signs, urine and blood) just prior to injection of the first eye (i.e., after the year of observation and at the time of crossover). For the remaining assessments, Control subjects' Year 1 analysis value prior to injection became the injection baseline value.

At the time of the BLA data cut-off for the efficacy analyses, (18-May-2016), all 20 (100%) Intervention subjects had completed the Year 2 study visit and all nine (100%) Control/Intervention subjects had completed the post-administration Year 1 study visit. In addition, five (25%) Intervention subjects had completed the Year 3 study visit and two (22%) Control/Intervention subjects had completed the post-administration Year 2 study visit.

8.2.1.1 Enrollment Criteria

A full list of inclusion and exclusion criteria are in Appendix 12.6. Based on the safety data from Phase 1, younger and less severely affected subjects were allowed to enroll in Phase 3. Key enrollment criteria for Phase 3 included the following:

- Subjects were to be three years of age or older with best-corrected VA worse than 20/60 and/or VF less than 20 degrees in any of 24 meridians as measured by III4e isopter or equivalent (in each eye).
- Molecular diagnosis, or confirmation of diagnosis of *RPE65* mutations (homozygous or heterozygous), by a CLIA-certified laboratory was required.
- Potential participants had to have sufficient viable retinal cells, defined as: 1) an area of retina within the posterior pole of > 100 micron thickness as shown on OCT; 2) ≥ 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole based on ophthalmoscopy; or 3) remaining VF within 30 degrees of fixation as measured by a III4e isopter or equivalent. Of note, all participants met the first criterion of > 100 micron thickness on OCT.

- Subjects who were able to pass the MLMT at Screening, in the time allotted, at the lowest illumination to be evaluated (1 lux) were considered too close to normal function with respect to ability to navigate in dim light conditions and were not eligible.
- Subjects who were unable to perform the MLMT at Screening with an accuracy score of ≤ 1 at the highest illumination to be evaluated (400 lux) were considered to have extensive disease progression such that they were less likely to achieve measurable, clinically meaningful benefit and were not eligible.

8.2.1.2 Phase 3 Endpoints

Considering the context of the clinical deficit specific to this disease and the need for a clinically meaningful endpoint to measure the subject's visual function, Spark Therapeutics developed the MLMT as a novel endpoint. The MLMT is detailed in Section 5 and Phase 3 endpoint selection is discussed in Section 6.5. Mobility testing in the earlier Phase 1 studies supports the feasibility of using this test of functional vision as an outcome measure, and the Mobility Test Validation Study (Section 5.4) established the construct and content validity of this test.

The primary endpoint was the treatment difference between Intervention and Control groups in mean bilateral MLMT score change at Year 1.

Secondary endpoints, hierarchically ranked, were treatment differences in:

- *Full-field light sensitivity threshold testing*: Averaged over both eyes for white light, change at Year 1 relative to Baseline
- *Monocular MLMT score change*: Change at Year 1 relative to Baseline for the first eye
- *Visual acuity*: Averaged over both eyes, change at Year 1 relative to Baseline

Additional endpoints included a visual function questionnaire, VF testing (Humphrey and Goldmann), community-based functional vision assessments (O&M), FST using blue and red light, contrast sensitivity testing and pupillometry.

Details of these testing procedures can be found in Section 6 and Appendix 12.2.

8.2.1.3 Primary Endpoint Evaluation

The overall MLMT procedure is described in Section 5.1. The testing rooms at the two study sites in Study 301 were established in parallel, using the same configuration of LED and incandescent lighting panels to achieve pre-set luminance levels. Mobility testing was videotaped and scored by masked, independent reviewers. The reviewers had received training both on the specific Mobility Testing Standard Operating Procedure and general orientation and mobility, and they were masked to randomization information or any other retinal/visual function test results. The sequence of video assessments (i.e., Baseline, Day 30, etc.) was also shuffled so that the graders did not know which time point they were assessing.

The light sensitivity cut-off at which the subject could not pass the test was identified at the Screening, Baseline, 30 Day, 90 Day, 180 Day, and 1 Year Visits. Randomization was stratified by Screening mobility passing level (≥ 125 lux or < 125 lux). At the first follow-up visit after

Baseline, mobility testing was carried out using the light sensitivity cut-off identified at Baseline and at lighting conditions just below this cut-off (sub-sensitivity cut-off light level). Subsequent follow-up visits were to use light levels at or below the Baseline level.

Inter-grader and intra-grader agreement data were monitored through quarterly quality assurance reports for all studies in the program using standardized MLMT, including the MTVS and Phase 3 studies (Table 17). Additionally, a sample of 10% of videos from the prior quarter was randomly selected to be re-graded, with a two-fold greater probability of selection for those videos in which collisions and/or penalties had been observed on grading. These videos were mixed with new videos provided to the graders, and graders were not informed that quality assurance was occurring or which videos were new. In the most recent mobility video grading QA report (28 August 2017), the "Final Pass/Fail" agreement was 97.9% for both the inter-grader agreement and consensus grade-regrade agreement, with more than 4000 videos evaluated to date (from this study as well as the Phase 1 studies and the Mobility Test Validation Study). Each MLMT run was analyzed by two of three masked graders trained in MLMT scoring by orientation and mobility experts through viewing video-recorded test runs. Analyses showed high agreement across the many continuous and binary pass/fail components of the MLMT.

Table 17: Consensus Scores and Intra-grader and Inter-grader Agreement for MLMT Results

		Inter-grader	Grade-regrade			
			Consensus	Grader #1	Grader #2	Grader #3
		n=4215	n=439	n=392	n=107	n=118
Intra-class Correlation	# Obstacles hit	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)	0.99 (0.99 - 1.00)	0.99 (0.99 - 0.99)
	# Times off-course	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)	0.98 (0.97 - 0.99)	0.99 (0.99 - 0.99)
	# Times re-guided	0.99 (0.99 - 0.99)	1.00 (1.00 - 1.00)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)	1.00 (1.00 - 1.00)
	# Tiles bypassed	0.91 (0.91 - 0.92)	0.89 (0.87 - 0.91)	0.92 (0.90 - 0.93)	0.94 (0.92 - 0.96)	0.95 (0.92 - 0.96)
	Obstacles plus Penalties	0.98 (0.98 - 0.98)	0.98 (0.97 - 0.98)	0.97 (0.97 - 0.98)	0.98 (0.98 - 0.99)	0.98 (0.97 - 0.99)
	Accuracy score	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)	0.99 (0.99 - 1.00)	0.99 (0.99 - 0.99)
	Course time	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)
	Time score	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)
Kappa	Course completed	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	0.67 (0.05 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)
	Accuracy Pass/Fail	0.95 (0.94 - 0.96)	0.93 (0.90 - 0.96)	0.91 (0.86 - 0.95)	0.96 (0.91 - 1.00)	0.91 (0.84 - 0.99)
	Time Pass/Fail	0.98 (0.98 - 0.99)	0.98 (0.96 - 1.00)	0.99 (0.98 - 1.00)	0.95 (0.88 - 1.00)	0.98 (0.94 - 1.00)
	Final Pass/Fail	0.95 (0.94 - 0.96)	0.94 (0.91 - 0.98)	0.92 (0.88 - 0.96)	0.96 (0.91 - 1.00)	0.93 (0.86 - 1.00)
n (%) Agree	Course completed	4215 (100.0%)	439 (100.0%)	391 (99.7%)	107 (100.0%)	118 (100.0%)
	Accuracy Pass/Fail	4115 (97 6%)	424 (96 6%)	374 (95.4%)	105 (98.1%)	113 (95.8%)
	Time Pass/Fail	4190 (99.4%)	435 (99.1%)	391 (99.7%)	105 (98.1%)	117 (99.2%)
	Final Pass/Fail	4126 (97 9%)	427 (97 3%)	377 (96 2%)	105 (98.1%)	114 (96.6%)

Note: Data from this table come from the Phase 1 and Phase 3 studies and the Mobility Test Validation Study

8.2.1.4 Statistical Analysis

Sample Size

Data from the eye injected in Study 102 were scored in a manner consistent with the mobility testing planned for the Phase 3 study. The distribution from the unilateral mobility testing in Study 102 showed an estimated mean ± standard deviation (SD) mobility testing score change in the intervention group of approximately 2 ± 1.74; the estimated median was 1.5. Eighty percent (80%) of subjects had a score change of 1 or higher; that is, if the Study 102 data were predictive of Phase 3, approximately 80% of subjects in the Intervention group were expected to demonstrate improvement in ability to navigate one year following gene therapy. Because of the degenerative nature of the disease and its slow progression, the Control group was expected to have a mean score change of zero.

Based on previous Phase 1 data, power calculations identified a minimum sample size total of 24 subjects (16 Intervention and 8 Control subjects) to yield a simulated power of greater than 90% to detect a clinically meaningful difference of one light level in the mobility test at a two-sided Type I error rate of 0.05, using a Wilcoxon rank sum test and corresponding exact *p*-value.

Randomization

Randomization, which occurred in a two-to-one ratio of Intervention to Control, used a block design stratified by age (≥ 10 years versus < 10 years) and MLMT passing level (pass at ≥ 125 lux versus < 125 lux) as determined at Screening.

Analysis of Primary and Secondary Endpoints

The analysis of the primary endpoint, the score change, used a non-parametric permutation test based on a Wilcoxon rank-sum as the observed test statistic and an exact method for the corresponding *p*-value. The approach is to randomize the allocation of treatment to subjects and, for a large number of replications, to calculate the test statistic from the Wilcoxon rank-sum test. The *p*-value from the permutation test is the proportion of *p*-values that are smaller than the value observed in the actual dataset. The primary endpoint was tested at a two-sided Type I error rate of 0.05.

To maintain strict control of the Type 1 error rate, the three secondary outcomes were tested in a hierarchical manner only to be formally tested if the primary outcome was statistically significant. The three secondary outcomes were also tested hierarchically at two-sided Type I error rates of 0.05. If FST was significant, monocular MLMT was tested; if monocular MLMT was significant, then VA was tested. Analyses of secondary endpoints FST and VA were based on longitudinal repeated measures models that provided estimates of the treatment difference in change at Year 1 relative to Baseline between the Intervention and Control groups. Analysis for monocular mobility testing (first eye) was analogous to the primary outcome.

8.2.2 Demographics

Demographics were consistent with the general patient population and similar across both treatment groups (Table 18). Overall, there were slightly more females than males, and subjects were primarily white and not Hispanic. At the time of randomization, the average subject was approximately 15 years old, with a range of four to 44 years.

Table 18: Demographic Characteristics in Study 301 (ITT)

Parameter/Category/Statistic	Intervention (N = 21)	Control (N = 10)
Age at Randomization (years)		
N	21	10
Mean (SD)	14.7 (11.8)	15.9 (9.5)
Range (min, max)	4, 44	4, 31
Quartiles (25th, median, 75th)	6, 11, 18	9, 14, 24
Male, n (%)	9 (43%)	4 (40%)
Race, n (%)		
White	14 (67%)	7 (70%)
Asian	3 (14%)	2 (20%)
American Indian or Alaska Native	2 (10%)	1 (10%)
Black or African American	2 (10%)	0
Ethnicity, n (%)		
Not Hispanic or Latino	16 (76%)	9 (90%)
Hispanic or Latino	5 (24%)	1 (10%)
Country of Residence, n (%)		
United States	17 (81%)	6 (60%)
Netherlands	1 (5%)	2 (20%)
Belgium	0	1 (10%)
Canada	1 (5%)	0
India	1 (5%)	0
Italy	0	1 (10%)
Mexico	1 (5%)	0

8.2.2.1 Ocular Disease Characteristics

The most common ocular history abnormalities at Baseline were nystagmus and retina abnormalities, which were reported in all (100%) subjects (Table 19). Strabismus was reported in eight (38%) Intervention subjects and five (50%) Control subjects; cataracts were reported in one (5%) Intervention subject and one (10%) Control subject.

Ophthalmic examinations of the cornea, anterior segment inflammation, posterior segment inflammation, intraocular pressure, retinal inflammation, and optic nerve were all Grade < 1 at Baseline. At Baseline, 97% of subjects presented with nystagmus on ophthalmic exam.

Most physical examinations revealed normal findings at Baseline; the most common abnormal body system at Baseline was the ears, nose, mouth, and throat, which was abnormal in 20% of Intervention subjects and 33% of Control subjects. No clinically significant abnormal physical exam was noted at Baseline.

Table 19: Ocular History in Phase 3 (ITT)

Abnormal ocular history, n (%)	Intervention (N = 21)		Control (N = 10)	
	First Eye	Second Eye	First Eye	Second Eye
Subjects reporting any abnormal ocular history	**21 (100%)**	**21 (100%)**	**10 (100%)**	**10 (100%)**
Subjects reporting				
Cataracts	1 (5%)	1 (5%)	1 (10%)	1 (10%)
Corneal opacities	0	0	0	0
Glaucoma	0	0	0	0
Keratoconus	0	0	0	0
Lenticular opacities	1 (5%)	1 (5%)	2 (20%)	1 (10%)
Nystagmus	21 (100%)	21 (100%)	10 (100%)	10 (100%)
Ocular malignancies	0	0	0	0
Retina abnormalities	21 (100%)	21 (100%)	10 (100%)	10 (100%)
Strabismus	8 (38%)	7 (33%)	5 (50%)	4 (40%)
Other	3 (14%)	1(5%)	2 (20%)	2 (20%)

8.2.3 Efficacy Results

Table 20 provides an overall summary of the pivotal Phase 3 efficacy results that are detailed in the subsequent sections.

Table 20: Summary of Pivotal Study 301 Efficacy Results, Year 1 Compared to Baseline

Analysis	Difference (95% CI) Intervention - Control	*p*-value	Analysis	Difference (95% CI) Intervention - Control	*p*-value
Primary and Supportive Efficacy					
Mobility Test Score Change			**Mobility Test Sum Score Change**		
Bilateral MLMT Score Change (ITT)	**1.6 (0.72, 2.41)**	**0.001**	MLMT Sum Score (ITT)	5.3 (3.11, 7.42)	< 0.001
Bilateral MLMT Score Change (mITT)	1.6 (0.76, 2.50)	0.004	MLMT Sum Score (mITT)	5.5 (3.35, 7.64)	< 0.001
Secondary and Supportive Efficacy					
Monocular Mobility Testing			**Visual Fields***		
MLMT Score Change 1st Eye (ITT)	**1.7 (0.89, 2.52)**	**0.001**	Goldmann VF III4e [sum total degrees] (ITT)	378.7 (145.5, 612.0)	0.006
MLMT Score Change 1st Eye (mITT)	1.8 (0.95, 2.61)	0.001	Humphrey VF, foveal sensitivity [dB] (ITT)	0.04 (-7.1, 7.2)	0.18
MLMT Score Change 2nd Eye (ITT)	2.0 (1.14, 2.85)	< 0.001	Humphrey VF, macula threshold [dB] (ITT)	7.9 (3.5, 12.2)	< 0.001
MLMT Score Change 2nd Eye (mITT)	2.1 (1.22, 2.96)	< 0.001			
			Visual Function Questionnaire*		
FST White Light [Log10(cd.s/m²)]			Subject; Year 1 (ITT)	2.4 (1.0, 3.8)	0.001
FST Averaged (ITT)	**-2.11 (-3.19, -1.04)**	**< 0.001**	Parent; Year 1 (ITT)	4.0 (2.1, 6.0)	0.002
FST Averaged (mITT)	-2.10 (-3.18, -1.02)	< 0.001			
FST 1st Eye (ITT)	-2.33 (-3.44, -1.22)	< 0.001	**Visual Acuity (Holladay) [LogMAR]**		
FST 1st Eye (mITT)	-2.32 (-3.43, -1.21)	< 0.001	**VA Averaged (ITT)**	**-0.16 (-0.41, 0.08)**	**0.17**
FST 2nd Eye (ITT)	-1.89 (-3.03, -0.75)	0.002	VA Averaged (mITT)	-0.13 (-0.37, 0.11)	0.27
FST 2nd Eye (mITT)	-1.88 (-3.01, -0.74)	0.002	VA 1st Eye (ITT)	-0.14 (-0.53, 0.25)	0.46
			VA 1st Eye (mITT)	-0.13 (-0.52, 0.26)	0.49
FST Blue Light [Log10(cd.s/m²)]*			VA 2nd Eye (ITT)	-0.13 (-0.28, 0.01)	0.072
FST Averaged (ITT)	-2.10 (-3.32, -0.88)	0.001	VA 2nd Eye (mITT)	-0.13 (-0.27, 0.02)	0.081
FST Averaged (mITT)	-2.09 (-3.32, -0.86)	0.002			
FST 1st Eye (ITT)	-2.08 (-3.32, -0.85)	0.002	**Visual Acuity (Lange) [LogMAR]***		
FST 1st Eye (mITT)	-2.06 (-3.31, -0.81)	0.002	VA Averaged (ITT)	-0.16 (-0.31, -0.01)	0.035
FST 2nd Eye (ITT)	-2.15 (-3.42, -0.88)	0.002	VA Averaged (mITT)	-0.15 (-0.29, -0.00)	0.047
FST 2nd Eye (mITT)	-2.14 (-3.42, -0.86)	0.002	VA 1st Eye (ITT)	-0.18 (-0.36, -0.01)	0.044
			VA 1st Eye (mITT))	-0.17 (-0.34, 0.01)	0.059
FST Red Light [Log10(cd.s/m²)]*			VA 2nd Eye (ITT)	-0.13 (-0.27, 0.01)	0.076
FST Averaged (ITT)	-1.46 (-2.06, -0.87)	< 0.001	VA 2nd Eye (mITT)	-0.13 (-0.27, 0.02)	0.081
FST Averaged (mITT)	-1.45 (-2.05, -0.85)	< 0.001			
FST 1st Eye (ITT)	-1.39 (-2.03, -0.76)	< 0.001			
FST 1st Eye (mITT)	-1.38 (-2.02, -0.75)	< 0.001			

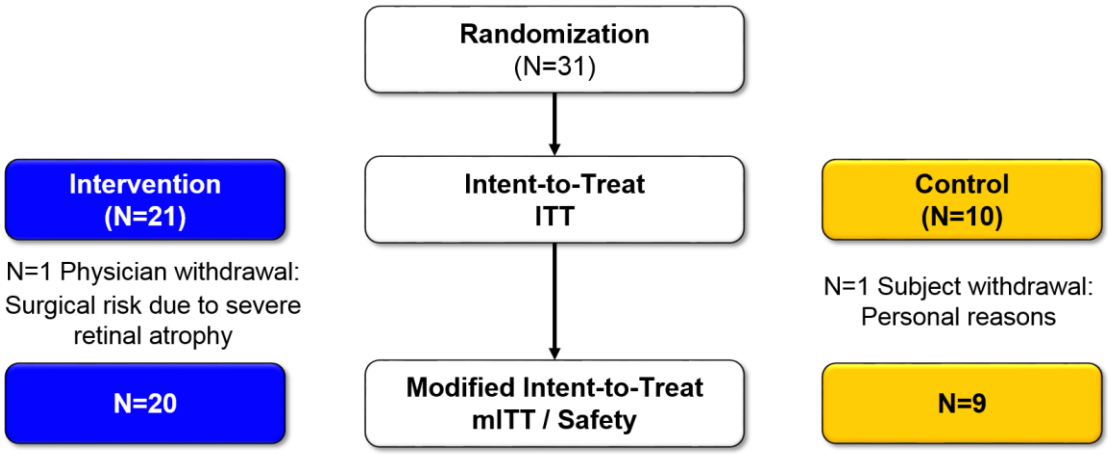
Analysis	Difference (95% CI) Intervention - Control	*p*-value	Analysis	Difference (95% CI) Intervention - Control	*p*-value
FST 2nd Eye (ITT)	-1.57 (-2.28, -0.85)	< 0.001			
FST 2nd Eye (mITT)	-1.54 (-2.26, -0.82)	< 0.001			

ITT = intent to treat; FST = full-field light sensitivity threshold; mITT = modified intent to treat; MLMT = multi-luminance mobility testing; dB = decibel; Log10(cd.s/m²) = logarithm of candela second per meter squared; LogMAR = logarithm of the minimum angle of resolution; VA = visual acuity; VF = visual fields. Cells for pre-specified primary and secondary analyses are shaded; **p*-values for additional endpoints, or supportive analyses of primary and secondary endpoints, are considered nominal. All *p*-values are 2-sided. MLMT permutation *p*-values were computed from all possible permutations; FST and VA, modeled results; VF and Visual Function Questionnaire, observed data and Wilcoxon rank-sum test.

8.2.3.1 Subject Disposition

The overall study enrollment included 21 subjects randomized to the Intervention group and 10 subjects randomized to the Control group (Figure 32). Of the 21 subjects in the Intervention group, 20 (95%) received bilateral injection of voretigene neparvovec, and one patient was withdrawn on randomization by the principal investigator prior to receiving voretigene neparvovec due to surgical risks related to severe retinal thinning. One subject in the Control group discontinued the study early (on randomization) due to personal reasons. Overall, of the 31 subjects randomized, 31 (100%) subjects were included in the ITT population, and 29 (94%) were included in the mITT and safety populations.

Figure 32: Subject Disposition in Study 301



8.2.3.2 Primary Endpoint – Multi-Luminance Mobility Testing

Enrolled patients ranged from mildly to severely impaired for both visual function and functional vison at Baseline. In Baseline mobility testing (a measure of functional vision), the lowest lux levels passed ranged from 4 to 400 lux (Table 21).

Table 21: Lowest Light Levels Passed at Baseline MLMT in Study 301 (ITT)

	Intervention (N = 21)			Control (N = 10)		
Lux level, n (%)	**First Eye**	**Second Eye**	**Bilateral**	**First Eye**	**Second Eye**	**Bilateral**
1	0	0	0	0	0	0
4	0	0	4 (19%)	1 (10%)	1 (10%)	1 (10%)
10	4 (19%)	7 (33%)	5 (24%)	0	2 (20%)	2 (20%)
50	10 (48%)	8 (38%)	7 (33%)	4 (40%)	1 (10%)	5 (50%)
125	2 (10%)	2 (10%)	3 (14%)	4 (40%)	4 (40%)	1 (10%)
250	1 (5%)	1 (5%)	0	0	1 (10%)	0
400	0	1 (5%)	0	0	0	0
>400*	4 (19%)	2 (10%)	2 (10%)	1 (10%)	1 (10%)	1 (10%)

*Unable to pass at 400 lux.

One Intervention subject and one Control subject had only Baseline data, since they withdrew from the study on the day of randomization and prior to any intervention. As specified in the Statistical Analysis Plan (SAP), these subjects were assigned (imputed) a score change of zero at Year 1 for both bilateral and unilateral mobility tests.

Study 301 demonstrated statistically significant results (Table 22). In the ITT population, the difference and 95% CI in mean MLMT bilateral score changes between the Intervention and Control groups was 1.6 (0.72, 2.41) light levels at Year 1 (p=0.001) where each 1.0 level represents the ability to complete the MLMT course when the light intensity is reduced by approximately a half-log.

This average change of almost two pre-specified light levels for the Intervention group reflects the gain of an ability to independently navigate using vision at a wider range of illuminance levels encountered in activities of daily living. On average, the Intervention group moved from passing the MLMT at the level of 50 lux, light found in an indoor stairwell or train station at night, to passing at the level of 4 lux, light associated with holiday lights or an outdoor parking lot at night.

Additionally, 13 of 20 (65%) of Intervention subjects who received voretigene neparvovec achieved the maximum possible MLMT improvement (passing at 1 lux) at one year, while no Control subjects passed at this light level, demonstrating significant improvement in functional vision at lower light levels after voretigene neparvovec.

Table 22: Bilateral MLMT Score Change: Year 1 Compared to Baseline in Study 301 (ITT)

MLMT Score Change	**Intervention (N = 21)**	**Control (N = 10)**	**Difference (95% CI) (Intervention-Control)**	**Permutation Test p-value**
Mean (SD)	1.8 (1.1)	0.2 (1.0)	1.6 (0.72, 2.41)	0.001
Range (min, max)	0, 4	-1, 2		
Quartiles (25th, median, 75th)	1, 2, 3	-1, 0, 1		

The permutation test p-value was computed from all possible permutations.

Consistent with the findings for the Intervention group in Study 301, Control/Intervention subjects showed a similar magnitude of response at Year 1 following crossover and treatment with voretigene neparvovec, with a mean (standard deviation [SD]) MLMT score change of 2.1 (1.6) light levels.

At Year 2, the Intervention subjects (n = 20) demonstrated durable improvements in the MLMT score change, with a mean (SD) score of 1.9 (1.1) light levels (see Figure 33, note that y-axis displays lux scores, i.e. score of 3 = 50 lux, 4 = 10 lux, 5 = 4 lux, 6 = 1 lux, see Section 5, Table 12). At Year 3, for the Intervention subjects with available data (n = 5), the MLMT score change appeared stable, with a mean (SD) of 2.0 (1.4) light levels. While only two Control/Intervention subjects had available post-injection Year 2 data, the score change appeared to be stable for these subjects. As shown in Figure 33, improvements in the MLMT bilateral lux score were evident by Day 30 following vector administration; these improvements were maintained out to Year 2, with observation ongoing.

Figure 33: Observed Mean Bilateral MLMT Lux Scores over Time in Phase 3 (mITT)

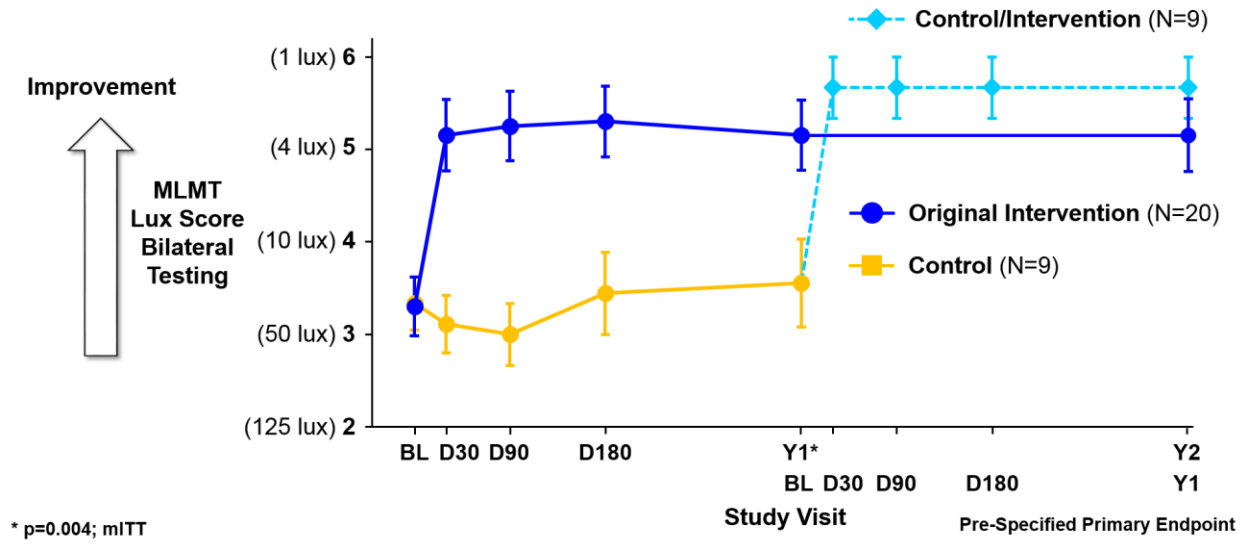
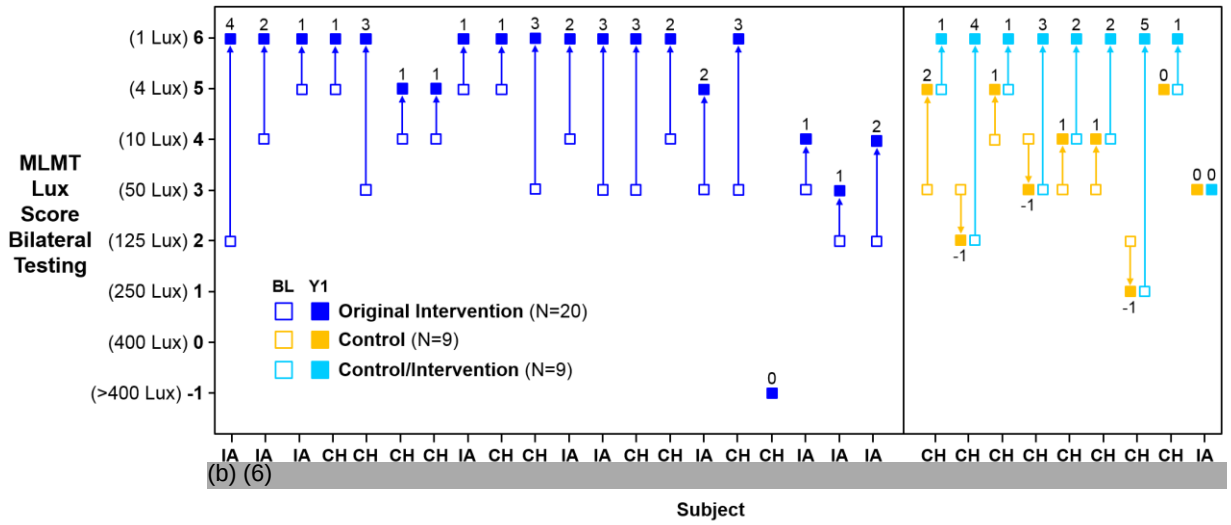


Figure 34 shows the individual bilateral MLMT lux scores at Baseline and Year 1 for the Original Intervention and Control groups. Results for the Control/Intervention group after crossover and through one-year post-injection are also shown.

Figure 34: Bilateral MLMT Lux Scores at Baseline and Year 1 by Subject in Phase 3 (mITT)



Score change is relative to baseline and displayed above or below the Year 1 lux score.

8.2.3.2.1 Supportive Analyses for the Primary Endpoint

As a supportive analysis, the MLMT sum score change was calculated by adding the respective MLMT score changes for the right eye, the left eye, and both eyes. For the ITT population, the mean (SD) MLMT sum score change was 5.8 (3.0) for the Intervention group and 0.5 (2.0) for the Control group, resulting in a mean difference (95% CI) of 5.3 (3.11, 7.42), which was statistically significant ($p < 0.001$) as seen in Table 23.

Nine of the 20 subjects (45%) in the Intervention group demonstrated the maximum possible MLMT sum score of 18 (i.e., passed at 1 lux for each individual eye and both eyes together).

Table 23: MLMT Sum Score Change: Year 1 Compared to Baseline in Study 301 (ITT)

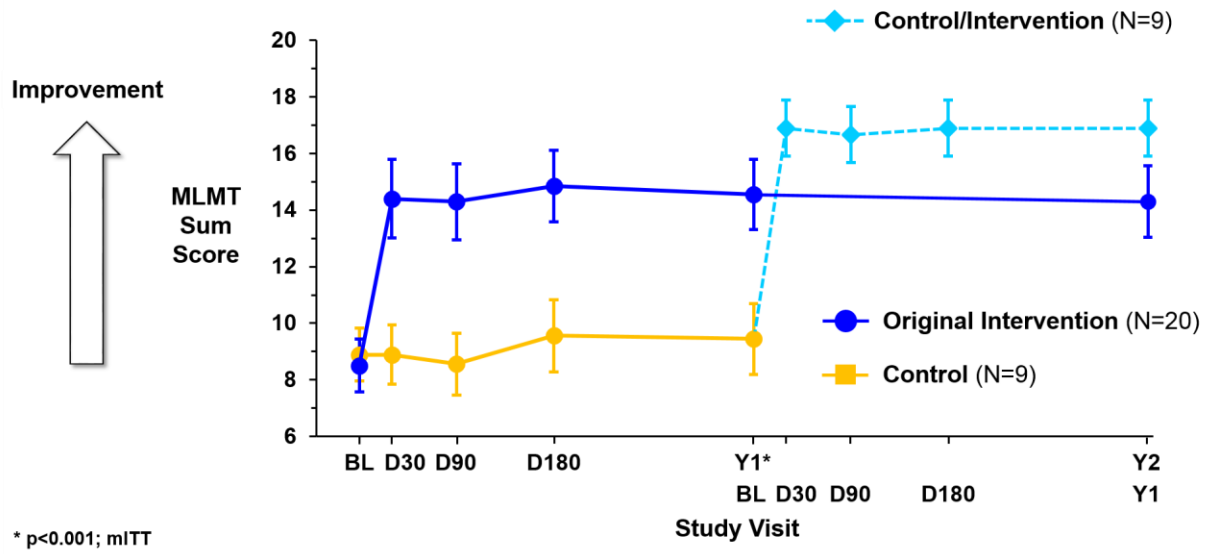
MLMT Sum Score Change	Intervention (N = 21)	Control (N = 10)	Difference (95% CI) (Intervention-Control)	Permutation test *p*-value
Mean (SD)	5.8 (3.0)	0.5 (2.0)	5.3 (3.11, 7.42)	< 0.001
Range (min, max)	0, 11	-3, 4		
Quartiles (25th, median, 75th)	4, 6, 7	0, 0, 1		

The permutation test *p*-value was computed from all possible permutations.

At Year 2, the Original Intervention group subjects (n = 20) continued to show durable improvements in the MLMT sum score change, with a mean (SD) of 5.8 (2.7) (Figure 35). At Year 3, for the Original Intervention subjects with available data (n = 5), the MLMT sum score change appeared stable, with a mean (SD) of 6.2 (4.4) (data not shown). These data were confirmed by results in the Control/Intervention group following crossover and injection. At Year 1 post-administration, the mean (SD) MLMT sum score change was 7.4 (4.4) for the

Control/Intervention group. For the two Control/Intervention subjects with available Year 2 data, the sum score changes also appeared to be stable.

Figure 35: Observed Mean MLMT Sum Scores Over Time in Phase 3 (mITT)



As an additional supportive analysis, the mean time to complete the MLMT averaged over all lux levels for the bilateral testing condition was performed and is shown in Table 24. The mean time to completion for the Intervention group decreased by 52.1 seconds on average at Year 1 compared to a decrease of 2.6 seconds in the Control group (post-hoc *p*-value: 0.001, mITT).

Table 24: MLMT Time to Completion, Averaged over Lux Levels (mITT)

	Intervention (N = 20)			Control (N = 9)			Year 1-Baseline	
Time to complete (sec)	**Baseline**	**Year 1**	**Change**	**Baseline**	**Year 1**	**Change**	**Difference (95% CI) (Intervention-Control)**	***p*-value**
Bilateral								
N	20	20	20	9	9	9		
Mean (SD)	101.1 (41.7)	49.0 (35.6)	-52.1 (38.1)	81.8 (20.8)	79.3 (20.3)	-2.6 (23.5)	-49.5 (-77.9, -21.2)	0.001
Range (min, max)	38, 179	16, 147	-145, 5	57, 124	54, 120	-32, 26		
Quartiles (25^{th}, med., 75^{th})	63, 91, 134	22, 33, 75	-67, -44, -29	66, 81, 91	64, 79, 92	-27, -9, 20		
Improved, n (%)			19 (95)			5 (56)		

All measures per person, per visit are averaged and then analyzed. The post-hoc *p*-value is from an ANOVA with change from baseline as the response variable and treatment group as a covariate.

8.2.3.3 Secondary Endpoints

8.2.3.3.1 Full-Field Light Sensitivity Threshold Testing (FST), white light

Modeled FST results for the ITT population are displayed in Table 25. The Intervention group had a mean change (SE) of -2.08 (0.29) log10(cd.s/m^2) at Year 1 while the Control group had a mean change (SE) of 0.04 (0.44). The modeled, mean treatment group difference (95% CI) was statistically significant with $p<0.001$ [-2.11 (-3.19, -1.04)].

Table 25: Modeled FST Estimates: White Light, in Phase 3 (ITT)

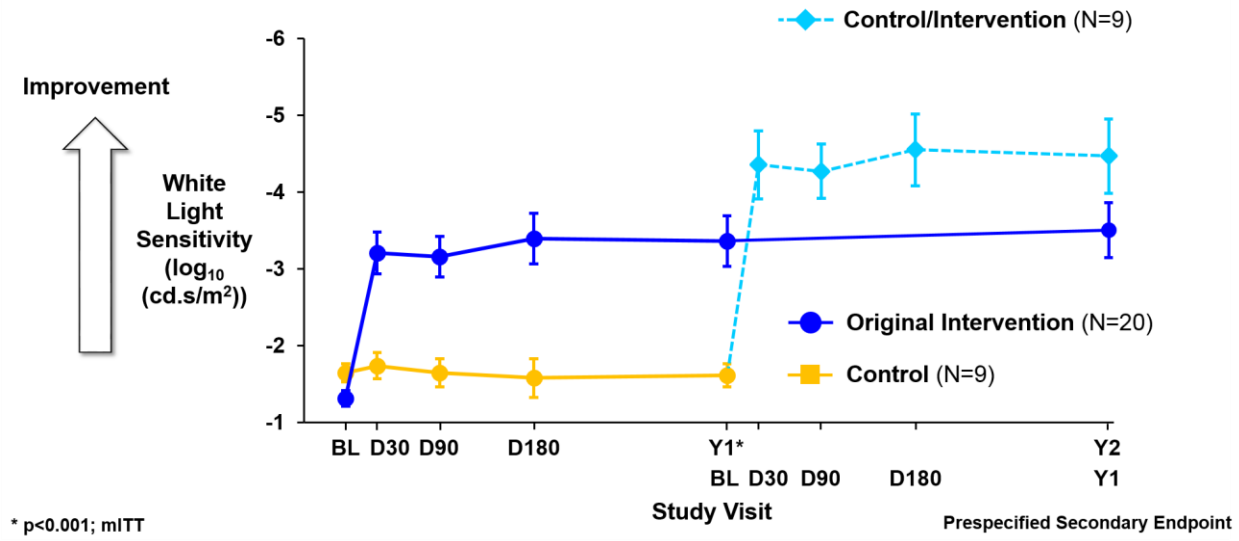
	Intervention N=21			**Control N=10**				
FST: white light [log10(cd.s/m^2)]	**Baseline**	**Year 1**	**Change**	**Baseline**	**Year 1**	**Change**	**Difference (95% CI) (Intervention-Control)**	***p*-value**
N	20	20	19	9	9	9		
Mean (SE)	-1.29 (0.09)	-3.36 (0.28)	-2.08 (0.29)	-1.65 (0.14)	-1.61 (0.42)	0.04 (0.44)	-2.11 (-3.19, -1.04)	< 0.001

All measures are averaged over both eyes and then analyzed.
Changes, 95% confidence intervals, and *p*-values were estimated using a repeated measures model with time, treatment, and time by treatment interaction.

Observed mean FST results (white light averaged over both eyes) can be seen in Figure 36 for the mITT population. At Year 1, the Intervention group improved by 2.10 (SD=1.58) log10(cd.s/m^2) on average. After crossing over, the Control/Intervention group improved by 2.86 (SD=1.49), on average, one year after receiving the injections. The benefits of voretigene neparvovec on FST were observed by Day 30 and continued throughout the first year of the study.

At Year 2, the mean change from Baseline was stable in the Original Intervention group, with a change of -2.27 (SD=1.65) log10(cd.s/m^2) in the mITT population. At Year 3, for the Original Intervention subjects with available data (n = 4), the mean change was -2.49 (SD=2.37) log10(cd.s/m^2) (data not shown). While only two Control/Intervention subjects had available Year 2 data, the values appeared to be stable for these subjects (data not shown).

Figure 36: Observed Mean FST White Light Over Time in Phase 3 (mITT)



8.2.3.3.2 Monocular MLMT Score Change

For the monocular MLMT score change for the first eye (ITT population), the mean (SD) change at Year 1 relative to Baseline was 1.9 (1.2) for the Intervention group and 0.2 (0.6) for the Control group, resulting in a statistically significant (p = 0.001) mean (95% CI) treatment effect of 1.7 (0.89, 2.52) light levels, similar to results observed with the bilateral MLMT testing condition.

8.2.3.3.3 Visual Acuity

In the ITT population for the secondary endpoint of VA averaged across both eyes using the Holladay scale for off-chart results, the modeled LogMAR changes reflected a mean improvement of 8 letters (i.e., ~1.5 lines) on the eye chart for Intervention subjects vs. a mean loss of about one letter for the Control subjects. The resulting modeled mean (95% CI) treatment difference of -0.16 (-0.41, 0.08) LogMAR was not statistically significant (p = 0.17).

In 2013, following the start of Study 301, both the European Medicines Agency (EMA) and the study's Data and Safety Monitoring Board (DSMB) expressed the opinion that the VA scale adapted from Holladay (2004), with estimates suggesting a difference of 1.0-log-unit step between counting fingers and hand motion perception, could present a biased estimate of any treatment effect (improvement or reduction in LogMAR) and recommended sensitivity analyses for VA using the scale proposed by Lange et al. (2009), in which the 1.0-log-unit step between counting fingers and hand motion is reduced to a 0.3-log-unit step.

Using the Lange et al. (2009) scale for off-chart VA results averaged across both eyes, the modeled mean (SE) change at Year 1 was -0.18 (0.04) LogMAR (an improvement of 9 letters) for the Intervention group and -0.02 (0.06) LogMAR (an improvement of 1 letter) for the Control group, resulting in a statistically significant (nominal p = 0.035, ITT) mean (95% CI) treatment difference of -0.16 (-0.31, -0.01) LogMAR.

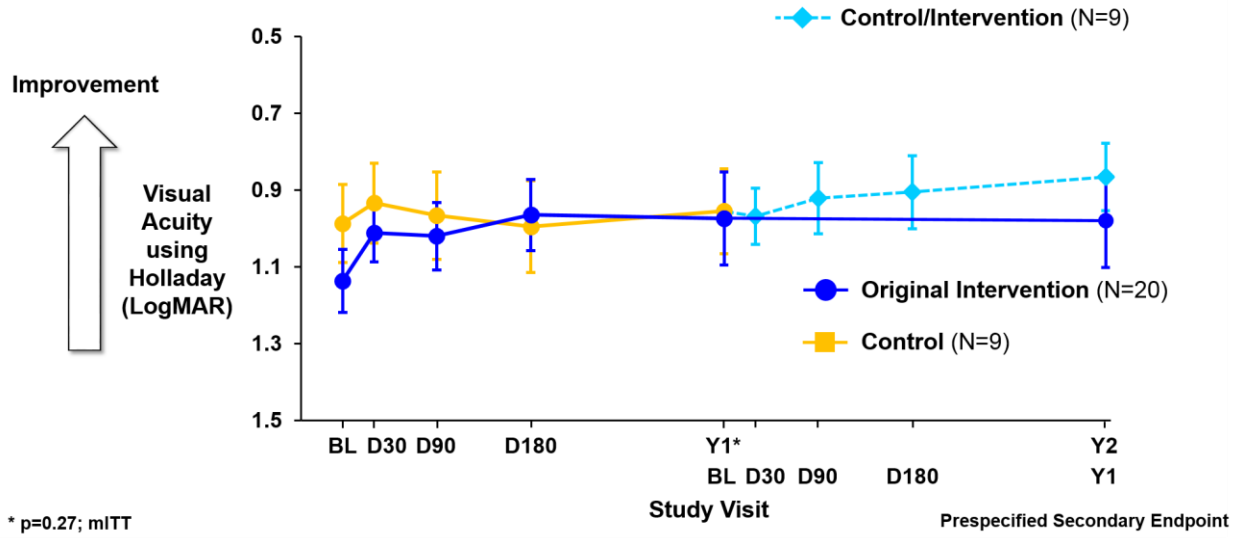
Considering the disease pathophysiology, it was predicted that VA would not change, although it would be a useful measure of safety. However, based on data generated in the small Phase 1 study, it seemed plausible that VA might improve, and thus it was included as the third of the ranked secondary endpoints (Table 26).

Table 26: VA Modeled Results, Year 1 Compared to Baseline, Using Holladay and Lange Scales in Phase 3

Analyses	Difference (95% CI) (Intervention change-Control change)	*p*-value
Holladay scale, LogMAR		
VA averaged (ITT)	**-0.16 (-0.41, 0.08)**	**0.17**
VA averaged (mITT)	-0.13 (-0.37, 0.11)	0.27
Lange scale, LogMAR		
VA averaged (ITT)	-0.16 (-0.31, -0.01)	0.035
VA averaged (mITT)	-0.15 (-0.29, -0.00)	0.047

Analysis of VA showed nonsignificant but durable changes in the Original Intervention subjects, with somewhat less pronounced changes in the Control/Intervention subjects following vector administration in the mITT population (Figure 37). More specifically, at Year 1, using the scale adapted from Holladay (2004) for any off-chart results, the mean (SD) changes from injection baseline were -0.16 (0.34) LogMAR (an 8-letter improvement) for the Original Intervention group and -0.09 (0.22) LogMAR (approximately a 5-letter (i.e., one line) improvement) for the Control/Intervention group, resulting in a -0.14 (0.30) LogMAR (a seven-letter improvement) mean change for the all-treated (n = 29) population. At Year 2, the change from injection baseline was stable in the Original Intervention group, with a change of -0.16 (0.36) LogMAR (an eight-letter improvement). At Year 3, for the Original Intervention subjects with available data (n=5), the change was 0.03 (0.66) LogMAR. While only two Control/Intervention subjects had available Year 2 data, the VA change from injection baseline appeared to be relatively stable from Year 1 for these subjects. Similar results were observed using either the Holladay (2004) or Lange et al. (2009) scales for off-chart values.

Figure 37: Observed Mean Visual Acuity over Time in Phase 3 (mITT)



8.2.3.4 Additional Endpoints

Additional endpoints included Visual Field Testing, a Visual Field Questionnaire, and a Community-based Functional Vision Assessment. Two additional exploratory endpoints, contrast sensitivity and pupillometry, were found to be noninformative and will not be discussed in this briefing document.

8.2.3.4.1 Visual Field Testing

Analysis of VFs using Goldmann perimetry testing in the ITT population showed an increase in the sum total degrees (see Section 6.4 for details on calculation) from Baseline to Year 1 for the Intervention group as compared to the Control group, indicating improved peripheral vision following injection with voretigene neparvovec (Table 27). More specifically, Goldmann VF III4e analysis showed a statistically significant treatment difference with a mean (95% CI) of 378.7 (145.5, 612.0) sum total degrees (nominal p=0.006; ITT).

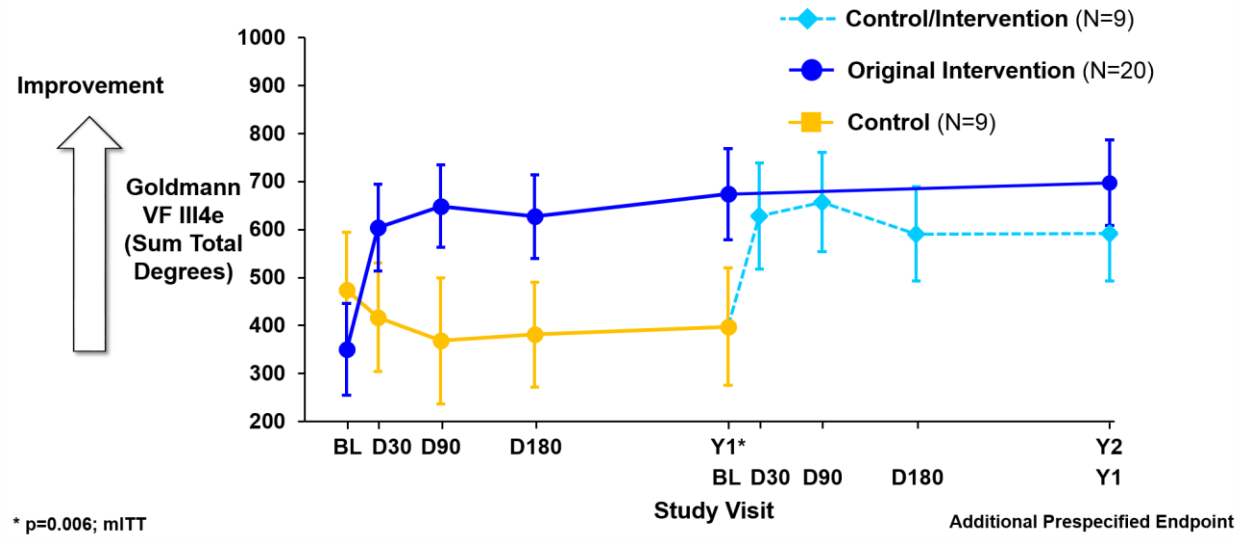
Table 27: Observed Mean Visual Field results at Baseline and Year 1 in Phase 3 (ITT)

	Intervention N=21			Control N=10			Year 1	
	Baseline	**Year 1**	**Change**	**Baseline**	**Year 1**	**Change**	**Difference (95% CI) (Intervention-Control)**	***p*-value**
Goldmann VF								
V4e (sum total degrees)								
N	20	11	10	10	5	5		
Mean (SD)	888.7 (487.8)	1032.8 (592.2)	78.8 (156.9)	788.2 (482.9)	778.8 (301.6)	-7.2 (341.4)	86.0 (-186.1, 358.1)	0.67
Range (min, max)	159, 1689	97, 1712	-146, 308	23, 1372	479, 1163	-504, 413		
Quartiles (25th, median, 75th)	443, 974, 1167	522, 1302, 1483	-62, 79, 227	318, 984, 1103	513, 731, 1009	-94, -33, 182		
III4e (sum total degrees)								
N	20	20	19	10	9	9		
Mean (SD)	332.9 (413.3)	673.9 (423.7)	302.1 (289.6)	427.1 (372.0)	397.8 (367.3)	-76.7 (258.7)	378.7 (145.5, 612.0)	0.006
Range (min, max)	0, 1418	0, 1405	-59, 820	0, 1042	45, 1144	-641, 218		
Quartiles (25th, median, 75th)	53, 153, 469	287, 592, 1045	19, 257, 520	109, 372, 686	105, 349, 474	-186, -4, 31		
Humphrey VF								
Foveal sensitivity (dB)								
N	20	20	19	10	9	9		
Mean (SD)	22.4 (6.8)	25.8 (9.1)	2.4 (9.7)	17.6 (8.9)	21.5 (8.9)	2.3 (5.3)	0.04 (-7.1, 7.2)	0.18
Range (min, max)	5, 32	0, 37	-24, 18	3, 28	6, 31	-3, 16		
Quartiles (25th, median, 75th)	19, 24, 27	21, 30, 32	-1, 5, 7	11, 17, 27	17, 26, 28	-1, 2, 3		
Mean macula threshold (dB)								
N	20	20	19	10	9	9		
Mean (SD)	16.1 (5.5)	24.0 (8.0)	7.7 (6.2)	14.4 (8.0)	15.8 (7.4)	-0.2 (1.7)	7.9 (3.5, 12.2)	<0.001
Range (min, max)	8, 26	2, 32	-8, 19	0, 22	2, 25	-2, 3		
Quartiles (25th, median, 75th)	12, 15, 21	19, 28, 29	4, 8, 13	10, 16, 22	13, 16, 21	-1, -1, 1		

Column header counts are subjects in the ITT population. All measures are averaged over both eyes and then analyzed. The observed two-sided *p*-value is from a Wilcoxon rank-sum test

Observed means over time are presented in Figure 38 for the mITT population. Overall, these mean gains with the more sensitive III4e target for both treatment groups are above the threshold of the reported 20% test-retest variability in Goldman VF, with an overall increase from injection baseline to Year 1 for the mITT population of approximately 73% for the 28 subjects evaluated, including an 86% increase for the Original Intervention group and a 49% increase for the Control/Intervention group. The increase in sum total degrees indicates an enlarged area of retinal sensitivity, attributable to increased photoreceptor function, which could translate into increased light sensitivity and improved peripheral vision. Note that the improvement in VF crossed the threshold of 500 sum total degrees observed in the Mobility Test Validation Study, which was associated with improved accuracy scores and MLMT performance.

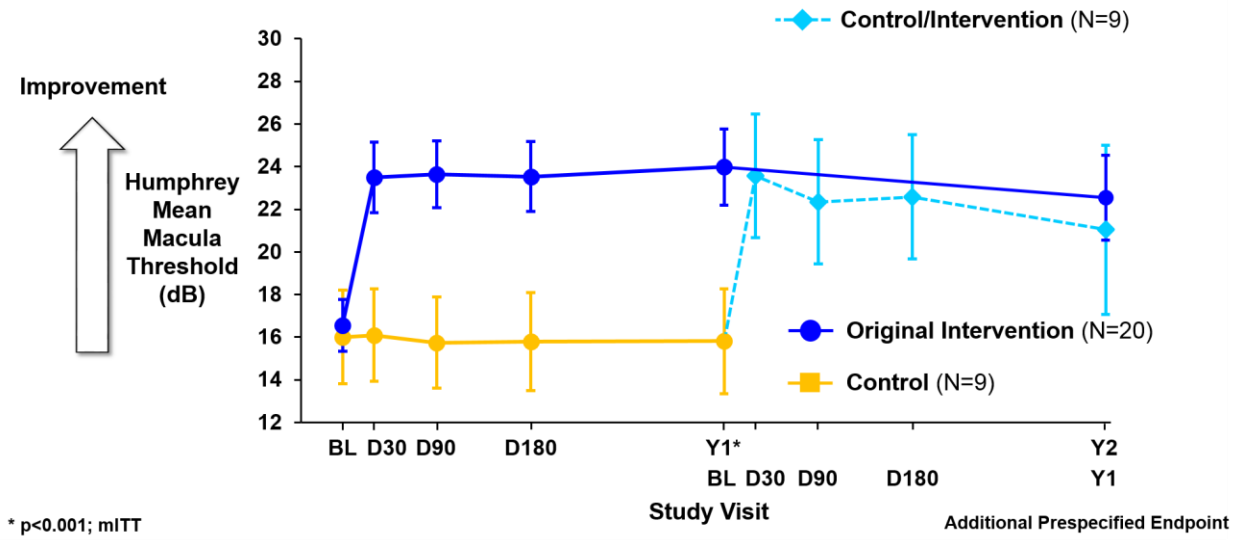
Figure 38: Observed Mean Visual Field Testing (Goldmann III4e) in Phase 3 (mITT)



For the Humphrey VF foveal sensitivity analysis, for which higher numbers (dB) equate to higher retinal sensitivity and testing used a FastPac test strategy with a size V test stimulus. Results are displayed in Table 27. After crossing over, the mean (SD) change from injection baseline at Year 1 was 3.2 (11.5) dB for the Control/Intervention group. At Year 2, the mean (SD) change in Humphrey VF foveal sensitivity was 3.1 (8.5) dB for the Original Intervention group (n=18) and 7.3 (3.2) dB for the two Control/Intervention subjects with available data.

Observed mean results for Humphrey VF mean macula threshold can be seen in Figure 39 for the mITT population.

Figure 39: Observed Humphrey Visual Field Mean Macula Threshold over Time (mITT)



For the Humphrey VF mean macula threshold analysis, the mean (SD) changes from injection baseline at Year 1 were 7.7 (6.2) dB for the Original Intervention group and 5.2 (9.9) dB for the Control/Intervention group. At Year 2, the mean (SD) changes in Humphrey VF macula threshold were 6.5 (7.4) dB for the Original Intervention group.

8.2.3.4.2 Visual Function Questionnaire

During the pivotal first year of Study 301, at each visit, both subjects and parents/guardians (if the subject was under 18 years old) completed a visual function questionnaire consisting of 25 questions pertaining to activities of daily living that are dependent upon vision or have a vision component. Subjects and parents responded about the perceived difficulty of these activities on a zero to 10 numerical scale (zero being the most difficult). The average of the responses determines the numerical score for each subject.

For both subject- and parent-completed surveys, the mean score of the Intervention group increased, indicating a reduction in the perceived difficulty of daily living activities, while the mean score of Controls did not change in the first year (Table 28). In the ITT population, the difference in mean change at Year 1 relative to Baseline between the two treatment groups was statistically significant for both subjects (mean [95% CI]: 2.4 [1.0, 3.8]; nominal p=0.001) and parents (mean [95% CI]: 4.0 [2.1, 6.0]; nominal p=0.002).

Table 28: Visual Function Questionnaire Average Scores (ITT)

Parameter/ Visit	Observed				Change from Baseline					
	Intervention N = 21		Control N = 10		Intervention N = 21		Control N = 10			
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	Difference (95% CI) (Intervention-Control)	*p*-value
Average score (subject)										
Baseline	21	4.4 (1.4)	9	4.9 (1.5)						
Day 30	20	6.3 (1.7)	9	4.8 (1.6)	20	1.8 (1.9)	9	-0.1 (0.9)		
Day 90	20	6.7 (1.7)	9	4.8 (1.4)	20	2.3 (1.7)	9	-0.2 (0.9)		
Day 180	20	6.7 (2.1)	9	4.7 (1.3)	20	2.2 (2.0)	9	-0.2 (1.1)		
Year 1	20	7.0 (1.9)	9	5.1 (1.8)	20	2.6 (1.8)	9	0.1 (1.4)	2.4 (1.0, 3.8)	0.001
Average score (parent)										
Baseline	15	3.6 (1.3)	5	3.3 (1.7)						
Day 30	15	6.7 (1.9)	5	3.4 (1.4)	15	3.1 (2.2)	5	0.1 (0.8)		
Day 90	15	6.9 (1.6)	5	3.3 (1.5)	15	3.3 (1.9)	5	0.0 (0.8)		
Day 180 [a]	14	7.3 (1.8)	5	3.4 (1.5)	14	3.5 (2.2)	5	0.2 (1.0)		
Year 1	15	7.5 (1.5)	5	3.1 (1.8)	15	3.9 (1.9)	5	-0.2 (1.3)	4.0 (2.1, 6.0)	0.002

Column header counts are subjects in the ITT population. The observed two-sided *p*-value is from a Wilcoxon rank-sum test.

8.2.3.4.3 Community-based Functional Vision Assessments (O&M Assessments)

Community-based functional vision assessments (also referred to as "Orientation and Mobility" or "O&M" assessments) were conducted yearly in the Phase 3 trial, although no formal analysis was planned. These narratives or case studies are informative in that they provide a "visual ability profile" which may be useful as a representation of actual visual performance in everyday life and activities of daily living.

Four highly skilled, trained evaluators performed yearly (Baseline, one-year and two-year follow-up) assessments in the subject's home environment and surrounding area, and the same evaluator (masked to randomization assignment) performed all assessments on a given subject. A total of 87 assessments were reviewed for the 29 mITT subjects. The assessments consisted of specific questions and tasks that enabled the evaluator to determine various visual abilities within the areas of basic visual skills, illumination, O&M observed tasks, mobility, and observed tasks related to activities of daily living.

In general, subjects who had improvements in the community-based functional assessments also showed improvements in MLMT scores. The MLMT clearly demonstrated improvement in navigation under low light levels after intervention; the general trend observed in the functional vision assessments suggests possible improvement in other areas as well, such as basic visual skills and activities of daily living.

This supports the clinical meaningfulness of the mobility test and suggests that subjects who demonstrate an improvement on the mobility test may also experience improved functioning in conducting activities of daily living within a 'real-world' setting.

8.3 Efficacy Conclusions

Results from the Phase 3 study demonstrate that bilateral near-simultaneous subretinal injection of voretigene neparvovec is an effective treatment option for patients suffering from vision loss due to biallelic *RPE65* mutation-associated retinal dystrophy. Consistent with the mechanism of action (restoration of enzyme activity), and the known kinetics of expression from an AAV2 vector, gains in functional vision (MLMT) and visual function (FST, VF) were seen within 30 days of vector administration. The pre-specified primary endpoint was met, demonstrating significant improvement in functional vision at lower light levels. Voretigene neparvovec administration also led to statistically significant improvements in visual function as measured by FST, and nominally significant improvements were also observed in Goldmann and Humphrey (macula threshold) VF exams.

Benefits observed throughout Year 1 in the Intervention group are further supported by similar results observed in the Control subjects following administration of voretigene neparvovec. Finally, improvements in visual performance were observed for at least two years following administration in the Intervention group, suggesting a durable response. Overall, the available clinical efficacy data support a consistent, clinically meaningful and durable treatment effect of voretigene neparvovec in patients with vision loss due to biallelic *RPE65* mutations.

9 CLINICAL SAFETY

Summary

- A single administration of voretigene neparvovec via subretinal injection in each eye demonstrated a safety profile consistent with vitrectomy and subretinal injection.
- The safety database includes 41 subjects in whom 81 eyes received voretigene neparvovec. Phase 1 subjects (n=12) have been followed for seven to nine years and Phase 3 subjects (n=29) have been followed for two to four years.
- Overall, AEs tended to occur early, and diminish and resolve over time.
- Most events were mild or moderate in severity and not related to therapy or the administration procedure.
- There were two ocular serious adverse events. One event of retinal disorder (loss of foveal function) assessed as related to the administration procedure; and one event of intraocular pressure increased in a subject with endophthalmitis who received anti-infectives and a periocular steroid injection.
- No deaths were reported during the clinical development program.
- Adverse events of special interest included all ocular adverse events. Of these, important identified risks include macular disorders, elevated intraocular pressure, retinal tear, intraocular infections and/or inflammation, and cataracts.
- 73% of patients reported having an ocular adverse event. Most ocular events resolved with minimal or no intervention. Many were known complications of intraocular surgery and most occurred during the first year of follow-up without sequelae.
- No deleterious immune responses were observed.
- Spark Therapeutics will implement a risk management plan to support appropriate administration and to collect long-term safety data.

9.1 Extent of Exposure

The clinical development program included 41 subjects in whom 81 eyes received voretigene neparvovec via subretinal injection (Table 29).

The Phase 1 program included 12 subjects in whom 23 eyes received voretigene neparovec. In study 101, the dose escalation study, 12 subjects received administration in a single eye, including three subjects at the proposed commercial dose. In Study 102, 11 of these 12 subjects received the proposed dose in the contralateral eye. One subject did not meet eligibility criteria for administration in the contralateral eye. In the Phase 3 study, 29 subjects underwent near-simultaneous bilateral administration of the proposed dose, seven to 14 days apart. In the

development program, only two subjects received the proposed dose at an interval other than seven to 14 days. In total, 72 eyes were administered the proposed dose of 1.5E11 vg.

Table 29: Subject Exposure to Voretigene Neparvovec

Study	Dose cohorts Number of subjects			Total number of eyes exposed	Total number of subjects exposed
Subretinal volume (microliters)	0.15 mL	0.15 mL	0.3 mL		
Dose (vector genomes)	1.5E10 vg	4.8E10 vg	1.5E11 vg		
Study 101 (First Eye)	3	6	3	12	12
Study 102 (Second Eye)	-	-	11[a]	11[a]	
Study 301 (Both Eyes) Original Intervention	-	-	20[b]	40	29
Study 301 (Both Eyes) Control / Intervention	-	-	9[b]	18	
Total				81	41

[a] One subject (high dose group) was not eligible for Study 102; 2nd eye did not receive voretigene neparvovec.

[b] Two subjects were discontinued before administration of voretigene neparvovec; one from the Intervention group and one from the Control group

All subjects in the clinical program were enrolled in a long-term follow-up study that will include 15 years of follow-up post administration. As of the data-lock point for the safety data, 5 May 2017, subjects from the Phase 1 studies have been followed for seven to nine years and subjects from the Phase 3 studies for two to four years (Table 30). No subjects have been lost to follow-up. Three subjects, one subject from each study, have elected for their annual follow-up visits to be conducted by phone call which includes completion of a clinical questionnaire and the Visual Function Questionnaire.

Table 30: Long-term Follow Up (Up to 120-Day Safety Update Data Cut-off 05-May-2017) – All Studies

Last Study Visit Completed	Study 101 N=1	Study 102 Subjects N=11 (Time from 101 admin)	Phase 1 Subjects N=12 (Time from 1st eye admin)	Study 301 Intervention N=20	Study 301 Control N=9	Phase 3 Subjects N=29	Total N=41
Year 1	1	11	12	20	9	29	41
Year 2	1	11	12	20	9	29	41
Year 3	1	11	12	20	2	22	34
Year 4	1	11	12	4	0	4	16
Year 5	1	11	12	0	0	0	12
Year 6	1	11	12	0	0	0	12
Year 7	1	11	12	0	0	0	12
Year 8	0	8	8	0	0	0	8
Year 9	0	2	2	0	0	0	2

9.2 Overall Adverse Events

Overall AEs following a single administration procedure per eye tended to occur early and diminish and resolve over time. Table 31 summarizes the percentage of subjects experiencing events across the clinical program. All subjects experienced at least one AE, and 85% of the AEs reported were of mild or moderate intensity. Six subjects experienced severe AEs, and there were 14 SAEs reported by nine subjects. None of the SAEs were assessed to be related to product, and most were unrelated to the administration procedure. All ocular adverse events were analyzed as AESIs (see Section 9.5). A total of 73% of subjects reported ocular AEs. The majority resolved with minimal or no intervention and without sequelae. No deaths were reported during the clinical development program or through the long-term follow-up.

Table 31: Overview of Adverse Events (Up to 120-Day Safety Update Data Cut-off 05-May-2017) – All Studies

Number (%) of Subjects	Phase 1			Phase 3					Total Phase 1 + Phase 3 (N = 41)[e]
				Study 301[a] (First Year of Study)		Study 301 / 302[b] (First Injection to 05-May-2017)		301 / 302[c] Original Intervention + Control / Intervention (N = 29)	
	101 (N = 12)	102 (N = 11)	Total Phase 1 (N = 12)[d]	Intervention (N = 20) 1st Injection to Year 1	Control (N = 9) Baseline to Year 1	Original Intervention (N = 20) 1st Injection to Data Cut-Off	Control / Intervention (N = 9) 1st Injection to Data Cut-Off		
with at least 1 TEAE	12 (100%)	11 (100%)	12 (100%)	20 (100%)	9 (100%)	20 (100%)	9 (100%)	29 (100%)	41 (100%)
with serious TEAEs	1 (8%)	4 (36%)	5 (42%)	2 (10%)	0	3 (15%)	1 (11%)	4 (14%)	9 (22%)
with TEAEs of maximum severity of									
mild	11 (92%)	4 (36%)	4 (33%)	4 (20%)	5 (56%)	4 (20%)	6 (67%)	10 (34%)	14 (34%)
moderate	1 (8%)	5 (45%)	6 (50%)	13 (65%)	4 (44%)	12 (60%)	3 (33%)	15 (52%)	21 (51%)
severe	0	2 (18%)	2 (17%)	3 (15%)	0	4 (20%)	0	4 (14%)	6 (15%)
with TEAEs related to the vector	0	0	0	0	NA[f]	0	3 (33%)	3 (10%)	3 (7%)
with TEAEs related to the administration procedure	10 (83%)	8 (73%)	10 (83%)	13 (65%)	NA[f]	13 (65%)	6 (67%)	19 (66%)	29 (71%)
with ocular TEAEs[g]	11 (92%)	9 (82%)	11 (92%)	12 (60%)	2 (22%)	12 (60%)	7 (78%)	19 (66%)	30 (73%)

a From injection through Year 1 (for Intervention subjects); from Baseline through one year of observation (for Control subjects). For Control subjects, events are technically not TEAEs as voretigene neparvovec was not administered until crossover (after one year of observation).
b For Intervention subjects, TEAE data from 1st injection to 05-May-2017; for Control / Intervention subjects, TEAE data from crossover/1st injection to 05-May-2017.
c Total TEAE data for all Phase 3 subjects from 1st injection / Baseline to 05-May-2017.
d Phase 1 TOTAL (N = 12) is calculated based on the number of unique subjects who were reported with at least one TEAE over the combined course of the Phase 1 studies.
e Phase 1 + Phase 3 TOTAL (N =41) is calculated as the sum of Phase 1 TOTAL and Phase 3 TOTAL, excluding pre-injection TEAEs in Controls.
f NA: Not applicable. Subjects in the Control group were not administered the vector and did not undergo a sham administration procedure, hence NA for related events. Ongoing AEs were only those unresolved up to data cut-off date, hence NA in Study 301.
g Number of subjects (not number of eyes); Ocular TEAEs are all TEAES coded under the SOC Eye Disorders, and certain TEAEs coded under the SOCs Investigations (e.g., intraocular pressure [IOP] increased), Infections and Infestations (e.g., conjunctivitis viral), and Injury, Poisoning and Procedural Complications (e.g., wound dehiscence); For Control subjects in 301 (before crossover), one event of photopsia (flashes of light) was documented as an ocular AE; one event of eye injury (contusion of left eyeball) was not included in the ocular AEs.

Adverse events occurring in ≥ 30% subjects who received voretigene neparvovec are summarized in Table 32. Across the clinical program, the most common AEs by System Organ Class (SOC) were Gastrointestinal Disorders, Eye Disorders, Nervous System Disorders, and Infections and Infestations. The most common TEAEs by preferred term (PT) were headache, leukocytosis, pyrexia, nasopharyngitis, nausea, cough, and vomiting.

Table 32: Adverse Events Occurring in ≥30% of Treated Subjects (Up to 120-Day Safety Update Data Cut-off 05-May-2017) – All Studies

	Voretigene Neparvovec Treated Subjects	
	Phase 1 7-9 years follow-up (N=12)	**Phase 3 2-4 years follow-up (N=29)**
Any AE	**12 (100%)**	**29 (100%)**
Headache	8 (67%)	13 (45%)
Leukocytosis	6 (50%)	11 (38%)
Pyrexia	8 (67%)	9 (31%)
Nasopharyngitis	8 (67%)	8 (28%)
Nausea	4 (33%)	10 (34%)
Vomiting	3 (25%)	10 (34%)
Cough	5 (42%)	8 (28%)

9.2.1 Severe Adverse Events

Most adverse events were mild or moderate in severity and not related to therapy or the administration procedure. In total, six subjects reported severe AEs and all were assessed as unrelated to voretigene neparvovec. One severe event is resolving, and all others resolved without sequelae.

From the Phase 1 studies, one subject reported a headache of severe intensity assessed by the investigator as not related to the administration procedure, and one subject reported an SAE of lower limb fracture during long-term follow-up assessed as not related to the administration.

In the Phase 3 study, one subject reported nausea and vomiting on the day of the procedure. This was assessed as related to the administration procedure, and resolved on the same day.

Three other subjects reported severe adverse events not related to voretigene neparvovec, the administration procedure, or the subjects' IRD. One subject experienced five severe AEs following administration of anesthesia for an oral surgery procedure. One subject with a history of complex seizure disorder experienced severe AEs of convulsion and ADR, the latter related to use of an anti-seizure medication, and two additional severe AEs of convulsion. A final subject experienced two severe AEs of menorrhagia and one of pneumonia, the latter of which is resolving. All of these events were also reported as SAEs (see below).

9.3 Serious Adverse Events

Table 33 summarizes the percentage of subjects with SAEs across the clinical program. There were 14 SAEs reported in 9 subjects across the Phase 1 and Phase 3 studies. One subject in Phase 3, with past medical history of complex seizure disorder, experienced a convulsion event

and ADR related to their anti-seizure medication, as well as two additional events of severe convulsion. One subject in Phase 3 experienced ADR to anesthesia received for oral surgery to remove a benign central odontogenic fibroma. Another subject from Phase 3 experienced two SAEs of menorrhagia and one of pneumonia. None of the 14 SAEs were assessed as related to the product, and 12 of 14 SAEs were unrelated to the administration procedure.

Table 33: Serious Adverse Events (Up to 120-Day Safety Update Data Cut-off 05-May-2017) – All Studies

	Voretigene Neparvovec Treated Subjects	
	Phase 1 7-9 years follow-up (N=12)	**Phase 3 2-4 years follow-up (N=29)**
Any SAE	5 (42%)	4* (14%)
Retinal Disorder	0	1
Intraocular Pressure Increased	1	0
Anal Fistula	1	0
Cryptochism	1	0
Paraesthesia	1	0
Lower Limb Fracture	1	0
Convulsion	0	1
Adverse Drug Reaction [a]	0	2
Menorrhagia	0	1
Pneumonia	0	1

*In Phase 3, one subject experienced SAEs of convulsion (3 events) and ADR, and one subject experienced SAEs of menorrhagia (2 events) and pneumonia.

[a] Includes one adverse drug reaction to anti-seizure medication for a pre-existing complex seizure disorder and one adverse drug reaction to anesthesia received during oral surgery.

Two subjects reported ocular SAEs. One was an event of retinal disorder in a subject from the Phase 3 study in the Control/Intervention group. The event of loss of foveal function was reported 34 days after vector administration. There was thinning of the central retina and a clinically meaningful loss in VA that did not resolve by one year. The event resolved with sequelae and was assessed to be related to the administration procedure.

The other ocular SAE was a case of intraocular pressure (IOP) increased in a subject from Study 102. The subject presented with signs and symptoms suggestive of endophthalmitis 11 days after the administration procedure which was reported as an adverse event and was treated with intraocular anti-infectives and a periocular steroid injection. The vitreous culture was positive for Staphylococcus epidermidis, and the event resolved 43 days after onset. Starting approximately three months after the administration of voretigene neparvovec, the IOP was persistently >30mmHg (compared to a normal range of approximately 10-20 mmHg), with measurements of >40 mmHg documented by the referring physician. The SAE of IOP increased and an AE of ongoing optic atrophy were reported at 151 days post-administration. This was assessed to be an adverse reaction related to the periocular steroid treatment.

9.4 Deaths

No deaths were reported during the clinical development program

9.5 Adverse Events of Special Interest

All ocular AEs were identified as AESIs. A total of 73% of patients reported having at least one ocular adverse event. The majority of the ocular AEs resolved with minimal or no intervention. Many are known complications of intraocular surgery and most occurred during the first year of follow-up and without sequelae.

Certain ocular AEs were identified as important risks because they were assessed as related to treatment, required clinical management, and impact the benefit-risk profile. These include macular disorders, intraocular pressure increased, retinal tear, intraocular infections and/or inflammation, and cataracts.

Events are summarized in Table 34.

Table 34: Ocular AESIs (Up to 120-Day Safety Update Data Cut-off 05-May-2017)

	Eyes (N=81)	Subjects (N=41)
Macular Disorders	9	7
Intraocular Pressure Increase	10	8
Retinal Tear	4	4
Intraocular Infections / Inflammation	5	3
Cataract	16	9

Macular disorders were reported in nine eyes in seven subjects (Table 35). These include events of macular hole, macular degeneration, eye disorder, maculopathy, and retinal disorder. Four of the events were unresolved at the time of data cut-off. These include one of the macular hole events and all three maculopathy events. One macular hole event and both retinal disorder events resolved with sequelae. Three events resolved without sequelae. All macular disorders were considered related to the procedure and none were considered related to the product.

Table 35: Ocular AESIs: Macular Disorders (Up to 120-Day Safety Update Data Cut-off 05-May-2017)

Preferred Term (verbatim)	Eyes (N=81)	Subjects (N=41)
Macular Disorders	**9**	**7**
Macular Hole	3	3
Macular Degeneration (Macular Thinning)	1	1
Eye Disorder (Foveal Dehiscence)	1	1
Maculopathy (Epiretinal Membrane, Macular Pucker)	3	2
Retinal Disorder (Foveal Thinning, Loss of Foveal Function)	2	1

There were 10 events of intraocular pressure increased reported in eight subjects. One event was serious (Section 9.3) and was assessed as an adverse reaction to a periocular steroid injection and not related to the vector or administration procedure. All events were mild or moderate in severity. Nine of the 10 events resolved without sequelae, and the unresolved event is in an eye that did not receive voretigene neparvovec administration. Most events were considered related to the administration procedure.

Four retinal tears were reported. The retinal tears were observed and repaired by the surgeon with laser retinopexy during the vector administration procedures. These events occurred in one Phase 1 subject and three Phase 3 subjects. All events were non-serious and resolved without sequelae. All events were considered related to the administration procedure and none were considered related to the product.

Intraocular infection and/or inflammation was reported in five eyes in three subjects. These events included one event of culture-positive endophthalmitis (Section 9.3). All events were considered non-serious, and all have resolved. All were assessed to be related to the administration procedure and not to the product.

Patients with IRDs have a higher incidence of cataract formation than the general population, and vitrectomy (part of the voretigene neparvovec administration procedure) is associated with a high incidence of cataract formation and/or progression. Sixteen events of cataract have been reported in nine subjects in the clinical program. All events were non-serious. Elective cataract extraction procedures have been performed for seven of the 16 events. Overall, there are nine eyes in five subjects with ongoing events of cataract. Most of these events were considered related to the administration procedure.

9.6 Other Safety Topics of Interest

In addition to the AESIs, safety topics of interest include retinal deposits, retinal thickness measurements by OCT imaging, decreased VA, as well as immunology data.

9.6.1 Retinal Deposits

There were three events of retinal deposits (verbatim subretinal precipitate) in one eye each of three subjects in the Control/Intervention group of the Phase 3 study. In two subjects, the event was in the first eye that received voretigene neparvovec, and in one subject it was the second eye. Onset occurred within one to six days after administration. All cases were mild in intensity, transient in nature, and resolved without intervention or sequelae within seven to 27 days. All were considered related to the product.

9.6.1 Retinal Thickness

Retinal thickness was assessed by optical coherence tomography imaging as a safety measure in the Phase 3 study. Thinning of the central retina was noted in the post-operative period with a mean change from injection baseline in foveal thickness at Day 30 of -24.4 µm across the all-treated Phase 3 mITT/safety study population (Baseline mean of 185.2 microns). Retinas returned to pre-treatment thickness by the Year 1 visit.

9.6.2 Decrease in Visual Acuity

In total, nine eyes in seven subjects had a clinically meaningful decrease in VA using the definition of at least 0.3 LogMAR worsening (representing at least a 15-letter or three-line loss on an eye chart) during the clinical development program. Four of the eyes had an onset of VA decline within one month after the surgical administration. However, three of these showed improvements in several other measures of visual function and functional vision. The other five eyes had an onset of VA decline at or after the first year. Three of these eyes showed

improvement in FST during that same time period, and the other two were stable on at least one other measure.

Two of these subjects experienced an SAE and are described in Section 9.3. Details about the other five subjects are described below.

Of these five subjects, four were from the Phase 1 study, and one was from the Phase 3 study. Of the four from the Phase 1 program, three received a lower dose (4.8E10 vg/eye) than that carried forward into Phase 3 (1.5E11 vg/eye, high-dose in Phase 1).

The first subject from the Phase 1 study presented with clinically significant optic disc drusen at Study 101 Baseline and was administered the middle dose of the three doses. There was a significant loss in VA at the Day 30 visit which has remained stable with slight improvement over the ensuing eight years.

The second subject was also administered the middle dose in Study 101. This subject showed an improvement in VA at Day 30 which remained stable for approximately three years after the administration. At the subsequent visit, approximately four years after the procedure, the VA decreased with progressive loss up through the most recent visit, approximately six years of cumulative follow-up after the procedure.

The third subject was also administered the middle dose in Study 101. This subject showed some decline in VA at Day 30 with some fluctuation through Year 1 at which time there was a three-line loss. Since then, the VA has remained stable through approximately six years of cumulative follow-up after the procedure.

The fourth subject, also from Phase 1, showed a decrease in VA in the second injected eye at the Study 102 Week 4 visit with continued decline through Year 1 after which it has been stable through Year 5. The Investigator has described expansion of RPE cell depigmentation in this subject with concomitant profound pathologic high myopia.

The last subject with a clinically meaningful decrease in VA was enrolled in the Intervention group of the Phase 3 study and showed a loss in VA for the first injected eye at the Day 90 visit with progressive loss at the Year 1 visit and then has remained stable through the Year 4 visit. The second injected eye had stable VA after the procedure through the Year 3 visit and subsequently had a loss of VA as well. Of the subjects in Phase 3, this subject had the greatest vision loss at the time of enrollment; she failed to pass the MLMT at 400 lux (although her accuracy score was <1, qualifying her for enrollment), and her VA was LogMAR 1.95/1.78 in the two eyes.

In summary, of the seven subjects who experienced a LogMAR worsening of 0.3 or more, two experienced SAEs, one of increased intraocular pressure and resulting optic atrophy, and the other of foveal thinning and loss of VA noted in the months immediately following surgery. Three others were administered doses lower than those carried forward into Phase 3. Of the remaining two, one was noted by the Investigator to have profound (-12) pathologic high myopia, which may have represented a risk factor, and the other presented with the most severe vision loss of the Phase 3 cohort at enrollment.

9.6.3 Immunology

No clinical inflammatory responses to the investigational product have been observed and no dose limiting toxicity was seen in the clinical program.

Biodistribution of vector and immune responses to both AAV capsid and RPE65 were tracked and no deleterious immune responses were observed. Using an AAV capsid ELISA, a rise in antibodies to AAV was documented in some subjects, but there were no clinical correlates of this finding. Also of note, the subjects who manifested a rise in AAV antibody titer did not necessarily have vector sequences detectable in serum or tears. IFN-γ ELISPOTs to AAV capsid and RPE65 were also tracked. Results were positive at isolated visits for some subjects, but without clinical correlates. Otherwise, IFN-γ ELISPOT for AAV capsid and RPE65 were negative at the time points evaluated.

9.7 Risk Management/Long-Term Safety and Post-Approval Monitoring

Safety risks will be mitigated by appropriate product labeling, warnings and precautions, and a medication guide for patients. These will include specific language on the usage, dosage, and administration of the product, as well as warnings and precautions regarding adverse reactions that have been observed with the administration procedure (including, specifically, eye inflammation (including endophthalmitis) and retinal tear, retinal disorders, and increased intraocular pressure). Patients will be counseled about specific warning signs and symptoms related to these events. Patients will also be counseled to avoid air travel, travel to high elevations, or swimming for a short time after the administration of voretigene neparvovec. Recommendations will also be made to avoid strenuous physical activity for a time after the administration, and to avoid driving or operating heavy machinery until visual disturbances have ended.

Spark has proposed risk management activities to monitor long-term safety of voretigene neparvovec and the administration procedure. This will include monitoring of standard gene therapy risks as outlined in the FDA Guidance for Industry: Gene Therapy Clinical Trials-Observing Subjects for Delayed Adverse Events, as well as adverse events of interest associated with voretigene neparvovec or the administration procedure.

All subjects in the clinical development program have been enrolled in a long-term follow-up study in which they will be followed for 15 years post vector administration. The study includes annual history, physical and ophthalmic examinations, blood tests, urinalysis, and retinal/visual function tests.

Additionally, a prospective, observational safety registry is planned to collect long-term safety data from all subjects treated with voretigene neparvovec in a commercial setting.

To support appropriate patient care, voretigene neparvovec will be administered in a limited number of Centers of Excellence associated with an active ophthalmology practice that treats patients with IRDs including *RPE65* mutation-associated retinal dystrophy. The centers will have access to medical retina specialists, vitreoretinal surgery expertise, and pharmacies adequately equipped and trained to handle the product. Voretigene neparvovec will only be supplied if healthcare professionals have completed a training program. For surgical staff, this will include a surgical training program on subretinal delivery of the product including an in-person workshop

with the Principal Investigators from the program with a multimedia presentation and wet lab hands-on training. Additionally, there will be a detailed surgeon manual with illustrations describing the subretinal injection procedure (Appendix 12.1). There will also be an in-person training program for pharmacists and other pharmacy personnel regarding the preparation of the product. The training program will include a manual with step-by-step written instructions and illustrations as provided with the submitted labeling materials.

9.8 Safety Conclusions

The safety profile of voretigene neparvovec is consistent with vitrectomy and the subretinal injection procedure. The safety profile includes subjects followed for up to nine years.

As would be expected from a single administration therapy, AEs tended to occur early and resolve over time. Most AEs were mild or moderate in severity. There were no deaths reported during the clinical development program, and no deleterious immune responses were observed.

There were two ocular SAEs reported, and both led to loss of VA. One event was related to the administration procedure and one was a known adverse reaction to a concomitant medication. Nine eyes in seven subjects across the clinical program developed visual acuity worsening of 0.3 LogMAR or more. However, six of the nine eyes showed improvement in one or more other tests of visual function and/or functional vision.

Spark Therapeutics will implement a risk management plan to support appropriate administration and to collect long-term, post-approval safety data. All subjects in the clinical development program will be followed for 15 years post-administration. A prospective, observational, long-term safety registry will follow newly treated patients for five years. These activities, combined with the restriction of availability of the product to Centers of Excellence, pharmacy training, and appropriate labeling and warnings, will help ensure safety of the product.

10 BENEFIT/RISK ASSESSMENT

Overall, the available clinical efficacy data to date support a durable treatment effect of voretigene neparvovec in subjects with biallelic *RPE65* mutation-associated retinal dystrophy.

Efficacy has been demonstrated in a pivotal, Phase 3 study, with supportive findings in two Phase 1 studies. In Study 301, subjects in the Original Intervention group demonstrated durable improvements in visual performance across multiple endpoints for at least two years following sequential bilateral voretigene neparvovec administration. The study met its pre-specified primary endpoint measuring functional vision, as subjects in the Intervention group showed significant improvement from Baseline on the MLMT compared to Controls after one year. Consistent with the mechanism of action of the gene product, and the kinetics of expression from AAV, improvements in the Intervention group were apparent as early as Day 30 and were sustained over the one year of observation, while Control subjects showed no improvement during this time. Subjects in the Control/Intervention group, once injected with voretigene neparvovec, demonstrated onset and durability in visual performance improvements similar to those observed in the Original Intervention group, through at least one year following sequential bilateral subretinal voretigene neparvovec administration. Overall, 27 of 29 subject who received voretigene neparvovec in the Phase 3 clinical trial demonstrated improvements in functional vision/visual function.

While the Phase 1 studies were designed primarily to assess the safety and tolerability of voretigene neparvovec, the durability of response across MLMT and FST support the long-term efficacy of voretigene neparvovec. The majority of subjects demonstrated improvements in visual function and functional vision for at least four years.

The Phase 3 study conducted in this clinical development program was the first randomized controlled trial for a gene therapy for genetic disease. In this study, compared to both the uninjected Control group and the pre-injection conditions of the Intervention group, voretigene neparvovec delivery to the subretinal space led to an improvement in the MLMT – a testing tool developed explicitly to evaluate efficacy in patients with rod-mediated IRDs where visual loss includes nyctalopia, decreased VA and decreased VF. In addition to the improvement in MLMT, injected subjects showed a two-log improvement in full-field light sensitivity, and a >50% improvement in visual fields based on Goldmann perimetry using the III4e test stimulus. Notably, the gain in VF occurred across a boundary that had been previously identified as a threshold above which performance on MLMT is predicted to improve. Further, a community-based functional vision assessment and visual function questionnaire suggested that the gains in visual function led to improved functioning in conducting activities of daily living within a "real-world" setting.

The available clinical safety data demonstrate a safety profile for voretigene neparvovec consistent with vitrectomy and the subretinal administration procedure through up to nine years of cumulative post administration follow-up.

The majority of AEs reported were of mild to moderate severity, non-serious, and transient in nature. Most of the ocular AEs were known complications of intraocular surgery and occurred during the initial year of post-administration follow-up. There were two ocular SAEs reported,

and both led to loss of VA; neither was associated with worsening in bilateral functional vision as assessed by mobility testing.

Patients with biallelic *RPE65* mutation-associated retinal dystrophy suffer from a severe, debilitating and progressive retinal disease that eventually leads to near total blindness that cannot be corrected by glasses or corrective surgery and there are no available treatments. The majority of individuals begin to experience serious manifestations before the age of 18, which can include functional vision loss that substantially limits life activities and affects patients' social, emotional, and physical well-being. These manifestations continue into adulthood, with progressive loss of functional vision and visual function.

In aggregate, the visual assessments conducted in the Phase 3 study for efficacy and safety provide a comprehensive and meaningful overview of total visual capacity, overall subject performance, and demonstrate a positive benefit-risk profile of voretigene. The plans for restricted use of the product to Centers of Excellence, training programs, and the proposed long-term safety monitoring provide a means to monitor long-term risks. This risk management plan balances the need for further safety data collection while allowing access to therapy for this very rare and life-limiting disorder. Given the serious and progressive nature of *RPE65* mutation-associated retinal dystrophy and the lack of available treatment options, the favorable effects of the observed treatment benefits are considered to outweigh any identified and potential risks for the proposed population.

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12 APPENDICES

12.1 Surgical Training Manual

IMPORTANT NOTE:

The purpose of this Surgical Training Manual is to provide information to surgical personnel on the administration of LUXTURNA (voretigene neparvovec) in accordance with the approved US Prescribing Information.

The information in this manual is correct as of [DATE]. If you have questions about the administration of LUXTURNA (voretigene neparvovec), please contact your Spark medical representative or call Spark Medical Affairs at 1-855-SPARKTX.

LUXTURNA is indicated for the treatment of patients with vision loss due to confirmed biallelic *RPE65* mutation-associated retinal dystrophy.

For complete information, please see the full US Prescribing Information for LUXTURNA provided with this manual and at www.LUXTURNA.com/USprescribinginformation.pdf.

1. PURPOSE OF THE SURGICAL TRAINING MANUAL

This Surgical Training Manual describes the materials and procedures necessary to perform subretinal injection of LUXTURNA (voretigene neparvovec). This manual does not describe procedures for performing standard 3-port pars plana vitrectomy (PPV). Only surgeons experienced in performing macular surgeries and trained in subretinal injection procedures should administer LUXTURNA. *This manual does not describe pharmacy procedures for preparing LUXTURNA for administration. Please see the Pharmacy Training Manual for LUXTURNA for information on pharmacy procedures for preparing LUXTURNA.*

LUXTURNA is delivered via subretinal injection using a commercially available subretinal injection cannula. Subretinal injection is performed after a PPV. LUXTURNA must only be administered by subretinal injection and must not be administered by intravitreal injection.

2. REQUIRED MATERIALS

The treatment center should have standard equipment and supplies used in vitreo-retinal surgery available in the operating room on the day of the procedure. All materials required for a standard PPV are to be provided by the treatment center.

In addition to these standard materials, the treatment center must also supply the items listed below and described further in the following sections:

- Subretinal injection cannulas
- Extension tubes
- Syringes

2.1. Subretinal injection cannula

Table 1 lists subretinal injection cannulas that have been tested in biocompatibility experiments for use with LUXTURNA. Each of these cannulas was commercially available

as of the date of this manual. If you have questions about cannulas for use in the administration of LUXTURNA, please contact your Spark medical representative or call Spark Medical Affairs at 1-855-SPARKTX. Figure 1 shows a representative subretinal injection cannula.

Table 1: Biocompatible Subretinal Injection Cannulas

Product Description	Manufacturer	Reference Number
PolyTip® cannula 25 g/38 g 25 g x 28 mm cannula with 38 g (0.12 mm) x 5 mm tip	MedOne Surgical, Inc. Sarasota FL	3219
De Juan/Awh subretinal injection cannula 25 g/41 g 41 g (0.10 mm) tip	Synergetics, Inc. USA - Bausch & Lomb, Inc. O'Fallon MO	12.03.25
Retinal hydrodissection cannula 20 g/39 g 20 g shaft with 39 g inner diameter flexible tip	Storz Ophthalmic - Bausch & Lomb, Inc. Rochester NY	ED7365

IMPORTANT: A backup subretinal injection cannula should be available for each administration of LUXTURNA (voretigene neparvovec).

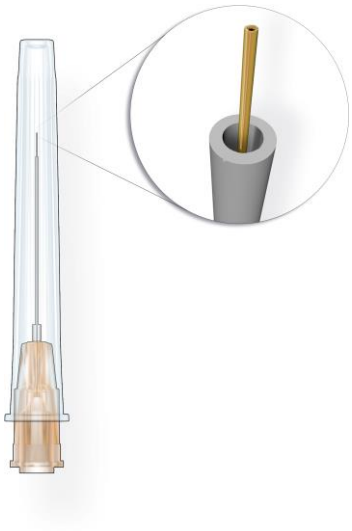


Figure 1: Representative subretinal injection cannula (model shown: PolyTip® cannula 25 g/38 g by MedOne Surgical, Inc., Sarasota FL; reference number 3219)

IMPORTANT: Ensure the subretinal injection cannula instrument gauge is no larger than the trocar size to be used in the PPV.

2.2. Extension tube

Table 2 lists extension tubes that have been tested in biocompatibility experiments for use with LUXTURNA (voretigene neparvovec). Each of the listed extension tubes was commercially available as of the date of this manual. If you have questions about extension

tubes for use in the administration of LUXTURNA, please contact your Spark medical representative or call Spark Medical Affairs at 1-855-SPARKTX. Figure 2 shows a representative extension tube.

Table 2: Biocompatible Extension Tubes

Product Description	Manufacturer	Reference Number
Ocular irrigation tube 6” (15.2 cm), ID 0.8 mm, OD 1.6 mm male/female Luer connections	Eagle Labs Rancho Cucamonga CA	169-30L-6
High pressure extension tube 6” (15.2 cm), ID 1.4 mm, OD 2.29 mm, PVC tube with male and female Luer lock connections	MedOne Surgical, Inc. Sarasota FL	3243

ID, inner diameter; OD, outer diameter

IMPORTANT: Use one of the recommended extension tubes. To avoid excess priming volume, do not use a tube longer than 6" (15.2 cm) or with an inner diameter greater than 1.4 mm.

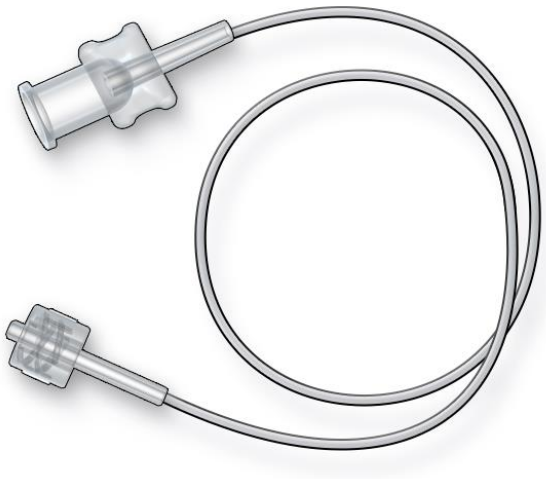


Figure 2: Representative extension tube (model shown: ocular irrigation tube by Eagle Labs, Rancho Cucamonga CA; reference number 169-30L-6)

2.3. Syringe

IMPORTANT:

- The pharmacy will prepare two syringes of LUXTURNA (voretigene neparvovec).
- One syringe will be used to administer the product and the second syringe will serve as a backup supply.
- Each 1-mL syringe will contain 0.8 mL of drug.
- Maintain the drug at room temperature until administration.
- Preparation of LUXTURNA should be performed within 4 hours of beginning the administration procedure.
- Following administration, all materials (including the backup syringe) should be discarded.
- Refer to local biosafety guidelines applicable for handling and disposal of the product.

Table 3 lists commercially available syringes that have been tested in biocompatibility experiments for use with LUXTURNA. Each of these syringes was commercially available as of the date of this manual. If you have questions about syringes for use in the administration of LUXTURNA, please contact your Spark medical representative or call Spark Medical Affairs at 1-855-SPARKTX. Figure 3 shows a representative syringe.

Table 3: Biocompatible Syringes

Product Description	Manufacturer	Reference Number
BD Luer-Lok™ 1-mL disposable syringe Has 1/100 mL graduation	Beckton, Dickinson & Company Franklin Lakes NJ	309628
Medallion® 1-mL syringe Fixed male Luer connector, flat grip	Merit Medical Systems, Inc. South Jordan UT	MSS011

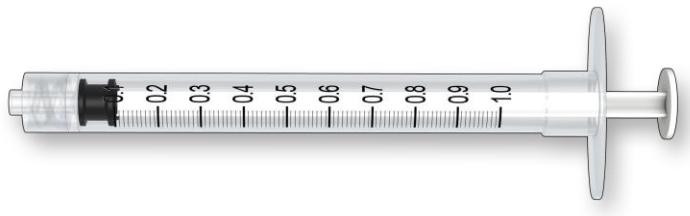


Figure 3: Representative syringe (model shown: BD Luer-Lok™ 1-mL disposable syringe, Franklin Lakes NJ; reference number 309628)

3. PROCEDURE

3.1. Surgical procedure overview

LUXTURNA should be administered in the surgical suite under controlled aseptic conditions. Once availability of the product from the pharmacy is confirmed, adequate anesthesia should be given to the patient prior to administration of LUXTURNA. The eye to be injected must be dilated and a broad-spectrum microbicide should be topically administered prior to the surgery according to standard medical practice.

3.1.1. Surgical team

Subretinal injection of LUXTURNA (voretigene neparvovec) requires coordination between a lead surgeon and an assistant (Figure 4). Effective communication between the surgical team members during the surgical procedure is required to ensure the appropriate administration of LUXTURNA. The lead surgeon and the assistant should agree upon communication signals for when to start injecting and when to stop.

- The lead surgeon will have primary responsibility for the procedure, including the following tasks:
  - Materials inspection
  - Injection apparatus assembly and preparation
  - PPV
  - Preparation of injection site
  - Insertion of the subretinal injection cannula into the retina during the subretinal injection procedure
  - Post-injection procedures
- The assistant will handle the syringe containing LUXTURNA during the subretinal injection procedure and control the speed of injection of the drug while the lead surgeon maintains the subretinal injection cannula in the proper position.

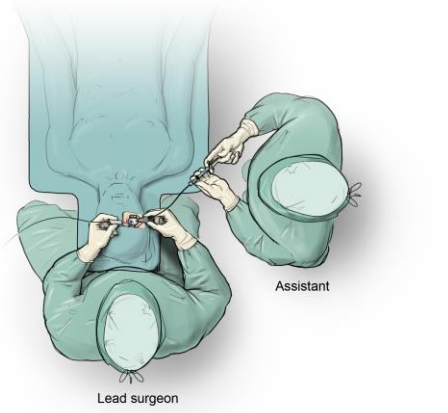


Figure 4: Lead surgeon and assistant positions in relation to patient (view without surgical microscope)

3.1.2. Surgical procedure components

Subretinal injection of LUXTURNA (voretigene neparvovec) requires that a PPV be performed prior to subretinal injection. The PPV should be carried out using standard surgical and medical procedures and is not described in detail in this manual.

3.1.3. Preoperative and postoperative procedures

In addition to standard preoperative and postoperative procedures, subretinal injection of LUXTURNA requires administration of an immunomodulatory regimen of prednisone.

Immediately prior to initiation of the immunomodulatory regimen and prior to administration of LUXTURNA, the patient must be evaluated for symptoms of active infectious disease of any nature. In case of such infection, the start of the immunomodulatory regimen and subsequent LUXTURNA (voretigene neparvovec) treatment must be postponed until after the patient has recovered.

Starting 3 days prior to the administration of LUXTURNA (voretigene neparvovec), an immunomodulatory regimen should be initiated following the schedule outlined in Table 4. Initiation of the immunomodulatory regimen for the second eye should follow the same schedule and supersede completion of the immunomodulatory regimen of the first eye. Patients will be on a systemic immunomodulatory regimen for a minimum of 18 days up to a maximum of 30 days, depending on the timing of the administration of LUXTURNA to the second eye.

Table 4: Preoperative and Postoperative Immunomodulatory Regimen*

Preoperative	3 days prior to administration	Prednisone (or equivalent) 1 mg/kg/day orally (maximum of 40 mg/day)
Postoperative	4 days (including the day of administration)	Prednisone (or equivalent) 1 mg/kg/day orally (maximum of 40 mg/day)
	Followed by up to 5 days, or until the beginning of second eye regimen, for the first eye *or* 5 days for the second eye	Prednisone (or equivalent) 0.5 mg/kg/day orally (maximum of 20 mg/day)
	Followed by 5 days of one dose every other day for the first eye only	Prednisone (or equivalent) 0.5 mg/kg orally every other day (maximum of 20 mg/day)

*Adjust dose of oral corticosteroids if necessary to manage side effects, such as weight gain, insomnia, or disturbance in blood glucose.

3.2. Materials inspection

1. In the operating room and prior to use, the lead surgeon should inspect the packaging of the subretinal injection cannula and the extension tube to ensure that sterility has not been compromised and the contents have not been damaged. If the tip of the cannula has been deformed, a new subretinal injection cannula must be used.
2. Prior to administration, the lead surgeon should inspect the LUXTURNA contained within the syringe. If particulates, cloudiness, or discoloration are visible, the syringe must not be used.

CAUTION: In the event that the subretinal injection cannula is damaged or compromised, DO NOT use the damaged cannula. Instead, inspect the backup subretinal injection cannula and, if not damaged or compromised, use the backup subretinal injection cannula for the procedure.

3.3. Injection apparatus assembly and preparation

Within the sterile field, connect the extension tube to the labeled syringe containing the diluted LUXTURNA (voretigene neparvovec) and to the subretinal injection cannula (Figure 5). Then fill the extension tube and subretinal injection cannula with diluted drug. Both the lead surgeon and the assistant will be in the sterile field during injection apparatus assembly and preparation.

3.3.1. Preparation of materials in the sterile field

1. On the sterile field, remove the subretinal injection cannula from its packaging and place on the sterile drape, leaving the clear plastic sheath covering the cannula tip in place.
2. Remove the extension tube from its packaging and place on the sterile drape.
3. Remove both syringes containing LUXTURNA from their packaging and place them on the sterile drape.

3.3.2. Assembly of the components

1. Attach the male Luer-Lok™ end of the extension tube to the subretinal injection cannula, leaving the clear plastic sheath covering the cannula in place (Figure 5).
2. Attach one syringe containing LUXTURNA to the female Luer-Lok™ hub of the extension tube.

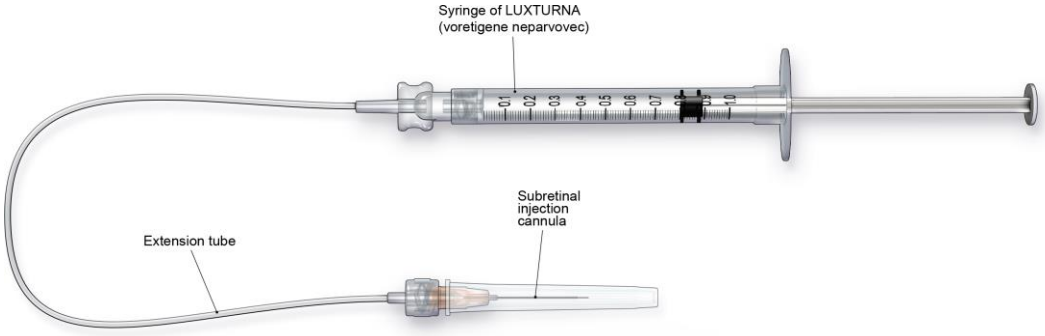


Figure 5: Injection apparatus assembly

3.3.3. Filling of the subretinal injection cannula in the sterile field over the sterile drape

1. Remove the plastic sheath from the tip of the subretinal injection cannula. Take care to avoid excess manipulation of the unsheathed cannula tip to avoid cannula deformation or damage.
2. Position the cannula tip over a sterile container.
3. Hold the syringe vertically with the Luer-Lok™ hub positioned upward, and slowly inject the LUXTURNA (voretigene neparvovec) into the extension tube and subretinal injection cannula. Continue injecting until 0.3 mL of LUXTURNA remains in the syringe, and the extension tube and the subretinal injection cannula are completely void of air. Ensure that the excess drug expelled from the cannula is released into a sterile container (Figure 6).

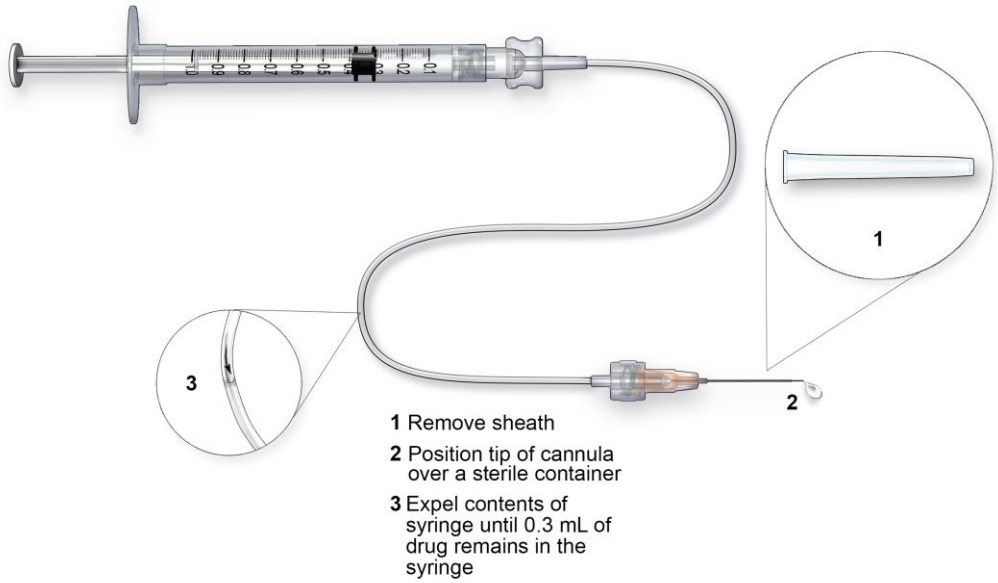


Figure 6: Filling of the subretinal injection cannula

4. Store the filled subretinal injection cannula in a sterile location until the time of subretinal injection.

IMPORTANT: Preparation of LUXTURNA should be performed within 4 hours of beginning the administration procedure.

3.4. Pars Plana Vitrectomy (PPV)

IMPORTANT: Avoid use of valved trocars to prevent damage to the subretinal injection cannula tip and to help prevent an increase in intraocular pressure (IOP) during the subretinal injection. If valved trocars are used, consider removing the valve cap or the trocar before insertion of the subretinal injection cannula.

1. Perform a 3-port PPV per the standard of care.

2. Trocar placement is per standard of care for macular surgeries.

IMPORTANT: Ensure that the vitreous is removed as completely as possible, particularly in the area of superior sclerotomy sites. Vitreous base removal with scleral depression is not necessary.

3. Induce a posterior vitreous detachment and assure that the posterior cortical vitreous is removed by standard means.

3.5. Preparation of injection site

3.5.1. Injection site inspection and preparation

1. Inspect the macular region and intended injection site.
2. Using a Tano Diamond Dusted Membrane Scraper (DDMS™; Synergetics USA, O'Fallon MO) or similar instrument, ensure that no vitreous remains over the macula or at the injection site.
3. If a visible epiretinal membrane (ERM) is present, the ERM should be removed according to standard procedures prior to subretinal injection.
4. Removal of internal limiting membrane is not recommended.

IMPORTANT: No dyes or triamcinolone were used to aid vitreous visualization or ERM removal during clinical trials of LUXTURNA (voretigene neparvovec).

3.5.2. Injection site selection

1. Select the injection site.
2. The injection site should be located along the superior vascular arcade, at least 2 mm distal to the center of the fovea (Figure 7).

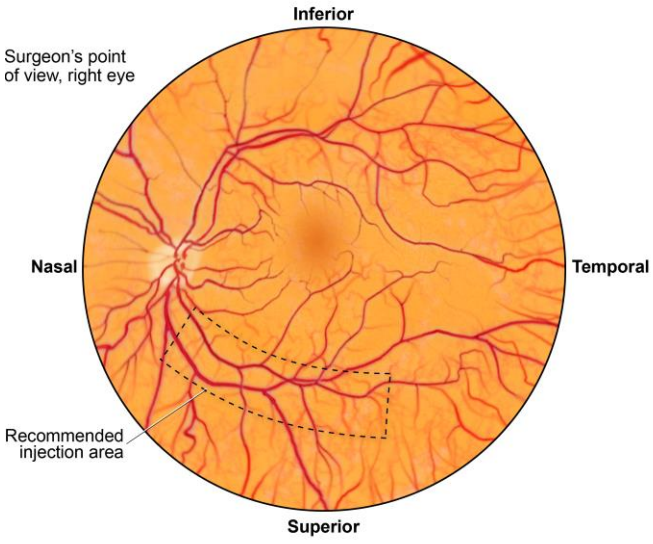


Figure 7. Recommended injection area

IMPORTANT: In the Phase 3 study, LUXTURNA (voretigene neparvovec) was injected at a site located ≥2 mm from the center of the fovea but posterior to the equator of the eye.

3. To determine the subretinal injection site location, consider the patient's retinal pathology and anatomy, and the ease of injection site accessibility.
4. The injection site should not be located within areas of pathologic or anatomic features that include the following examples:
   - Intraretinal pigment migration
   - Dense atrophy
5. To prevent bleeding complications, the injection site should avoid injury to retinal arteries/arterioles. However, placement of the tip of the cannula near a vein may allow the vein to serve as a visual reference point during the subretinal injection, with minimum risk of significant hemorrhage.

3.6. Subretinal injection procedure

1. Reduce the intraocular pressure to 10 mm Hg to accommodate the additional intraocular volume (0.3 mL) of LUXTURNA (voretigene neparvovec).
2. The assistant should retrieve the injection assembly from the sterile drape and, retaining hold of the syringe, hand the subretinal injection cannula to the lead surgeon.

IMPORTANT: Effective and ongoing communication between the lead surgeon and assistant is important to procedural success.

3. Ensure that the subretinal injection cannula and the syringe containing LUXTURNA are each properly locked to the extension tube.
4. Confirm that the tip of the plunger in the syringe is set at 0.3 mL.
5. The lead surgeon should insert the tip of the subretinal injection cannula through the vitrectomy trocar (Figure 8).

IMPORTANT: Take care not to bend the tip of the cannula during insertion.

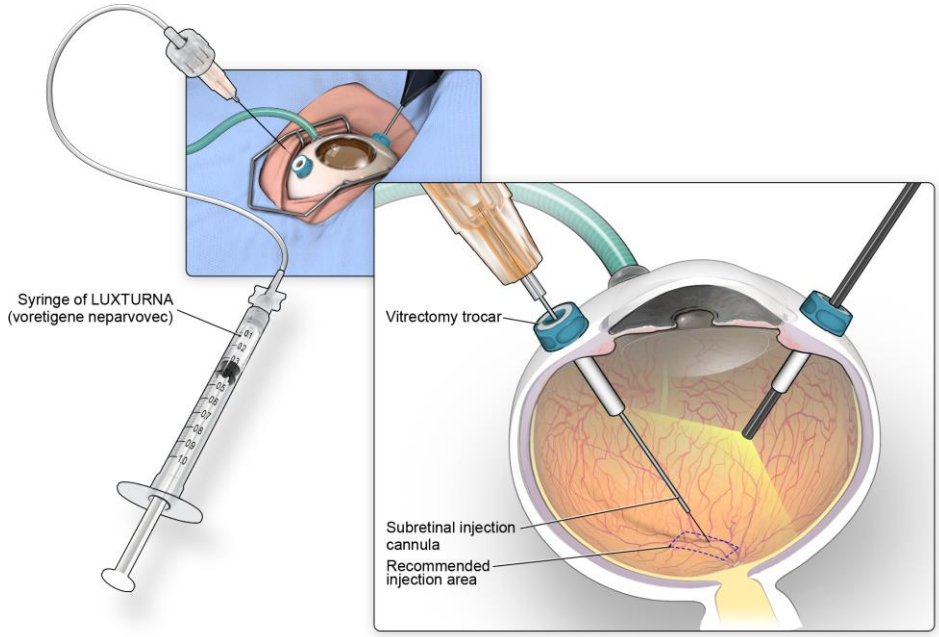


Figure 8. Insertion of subretinal injection cannula into the vitrectomy trocar

6. Direct the subretinal injection cannula to the injection site (Figure 9).

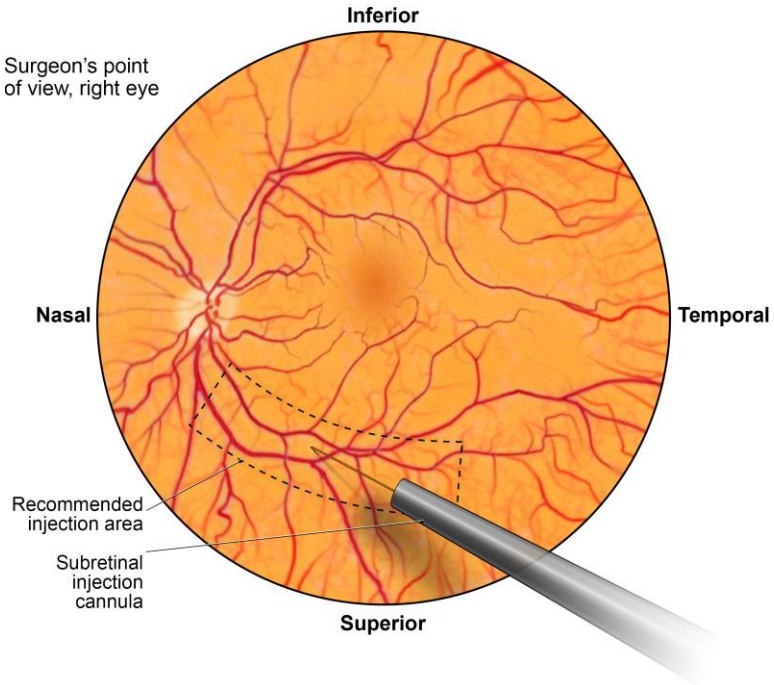


Figure 9. Subretinal injection cannula approaching injection site

7. Carefully position the tip of the subretinal injection cannula so as to indent the neural retina and drape the retina over the tip of the cannula, taking care not to perforate the retina (Figure 10).

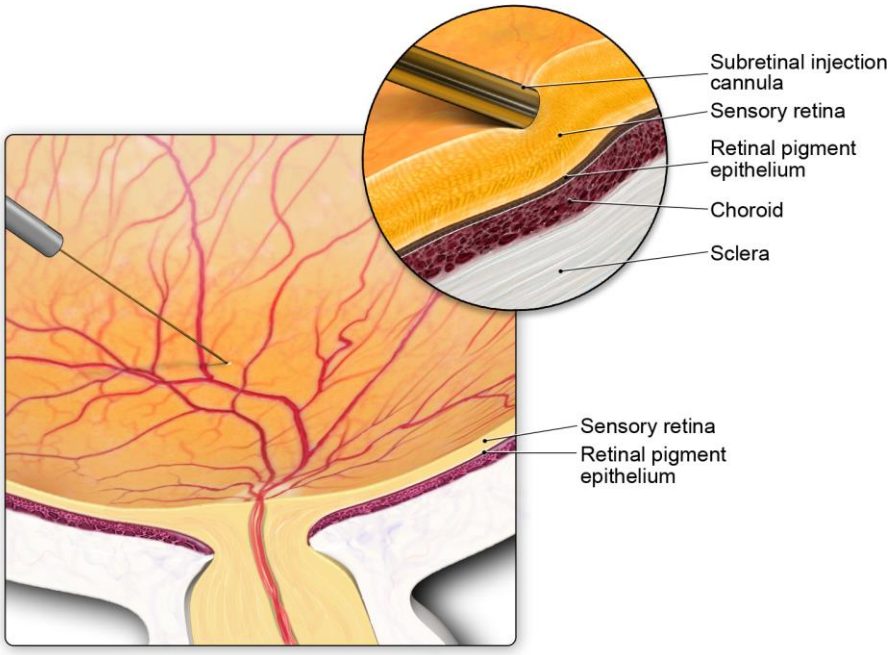


Figure 10. Placement of subretinal injection cannula for injection

IMPORTANT: The assistant must wait for verbal communication from the lead surgeon before depressing the plunger to initiate the injection.

8. The lead surgeon should instruct the assistant to begin slowly and steadily injecting LUXTURNA (voretigene neparvovec), while the lead surgeon observes for initial bleb formation (Figure 11).

IMPORTANT: Any resistance detected by the assistant while pushing the plunger should be communicated to the lead surgeon. Resistance may indicate a blockage in the injection apparatus assembly or misplacement of the cannula tip.

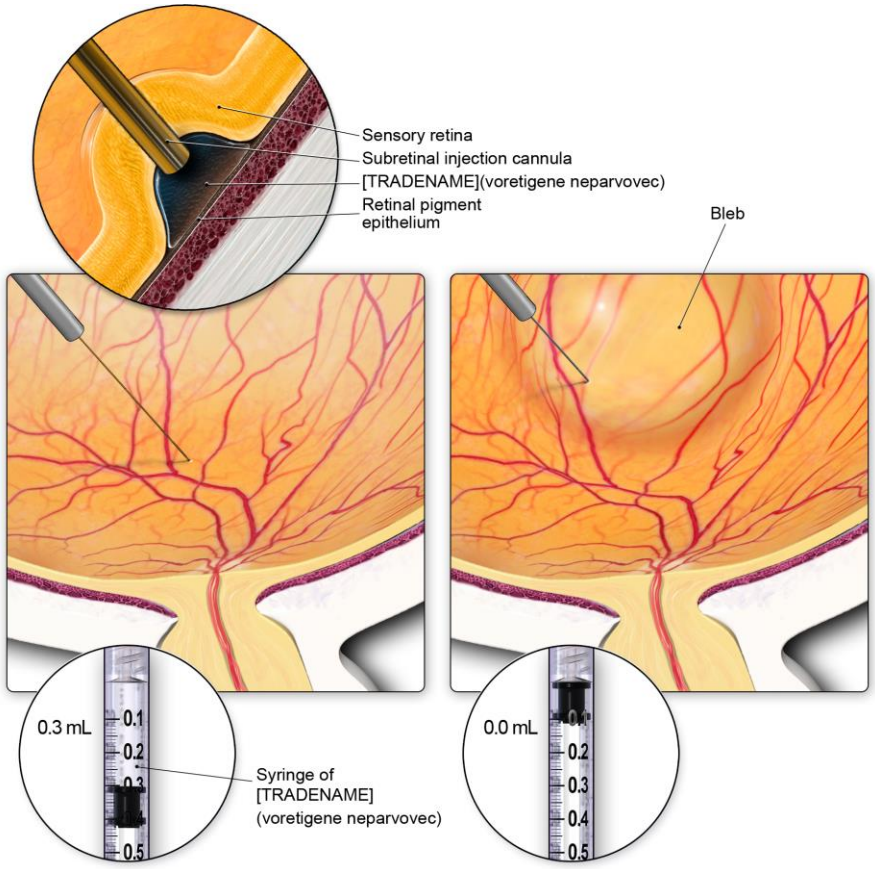


Figure 11: Subretinal injection and bleb formation

9. If a bleb does not begin to form:
   - Stop injection and confirm patency of the subretinal injection cannula.
   - If patency is confirmed, redirect the cannula tip to a different injection site within the recommended area.
   - Attempt subretinal injection of the remaining drug into the new site.
10. If a bleb begins to form, continue slowly injecting the full 0.3 mL of LUXTURNA (voretigene neparvovec). The assistant should hold the plunger down for approximately 5 seconds after completing the injection to ensure that the product has exited the subretinal injection cannula.

IMPORTANT: The shape of the bleb and the duration of time required for bleb formation will vary among patients.

   - In the event that bleb formation is successful, but only partial delivery of the full 0.3 mL to the subretinal space is accomplished, inject the remainder of the 0.3 mL at a different appropriate injection site.
11. Upon completion of administration, remove the subretinal injection cannula from the eye.

- Discard the subretinal injection cannula and syringe according to standard operating procedures.

3.7. Post-injection procedures

1. Increase intraocular pressure to 30 mm Hg.
2. Perform a comprehensive retinal examination using indirect ophthalmoscopy, and scleral indentation to evaluate for any retinal abnormalities. Treat any noted abnormalities as per standard of medical care.
3. Perform a fluid-air exchange in the vitreous cavity in order to remove any LUXTURNA (voretigene neparvovec) that may have refluxed from the subretinal injection site (retinotomy) and to provide tamponade. Carefully avoid fluid drainage near the retinotomy created for the subretinal injection.

IMPORTANT: Do not position the tip of the aspiration cannula in the immediate vicinity of the injection site, in order to prevent removal of the drug from the subretinal space.

4. Withdraw all instruments and vitrectomy trocars.
5. Supine head positioning is initiated immediately in the postoperative period and, upon discharge, the patient should be advised to rest in a supine position as much as possible for 24 hours.

12.2 Visual Assessments

12.2.1 Full-Field Light Sensitivity Threshold Testing

Full-field light sensitivity threshold testing assesses light sensitivity of the entire retina by measuring the subject's perception of different luminance levels (i.e., differing levels of light brightness), and is a subjective physiological test of retinal function relevant to the visual deficit experienced by patients with *RPE65* mutation-associated retinal dystrophy. To perform FST testing, the subject's eyes are dilated and then double patched in a dark room for 40 minutes for dark adaptation. After this, each eye is tested individually, keeping the contralateral eye patched. The subject's chin is placed on a chin rest in front of a Ganzfeld dome (a 40-cm diameter dome-shaped white screen). When testing commences, a light flashes inside the entire dome accompanied by a beeping sound. Each time a beep sounds the subject must indicate whether or not they saw a light by pressing a "yes" or "no" button. Light flashes continue at different intensities and an algorithm identifies the minimum luminance (brightness) at which the subject reliably perceives light. In the Phase 3 study, subjects were tested using white, red, and blue light stimuli for each eye separately.

Unlike many other tests of visual function, FST testing is not affected by nystagmus. Additionally, FST testing has an extensive dynamic range, which allows it to be used to evaluate both individuals with normal vision, or lesser degrees of impairment, and those individuals with more profound visual disability. In addition, this test measures overall visual function of the eye being tested and does not incorporate the sampling bias inherent in tests that evaluate specific areas of retina/vision and then extrapolate the findings to overall visual function.

FST testing is a relevant measure to assess the recognized visual disability known as nyctalopia, or night blindness, experienced by the vast majority of patients with *RPE65* mutation-associated retinal dystrophy. FST measures the threshold, or limits of light brightness that can be seen, to determine the sensitivity of the visual system; threshold is the reciprocal of sensitivity (i.e., low threshold equals high sensitivity). Changes in light sensitivity, reflective of photoreceptor function, can be tracked over time. Results are measured in relative units (decibels or dB), which are converted to absolute units (candela second per square meter or $cd.s/m^2$) to allow comparison across sites and subjects. The metric for analysis uses $log10(cd.s/m^2)$. For $log10(cd.s/m^2)$, a more negative result equals a lower threshold and thus improved light sensitivity, indicating improved photoreceptor function. This endpoint evaluates the ability of subjects to detect light as mediated by the photoreceptors affected in IRD associated with biallelic *RPE65* mutations; significant improvement in light sensitivity demonstrates that the visual pathway of associated photoreceptors is favorably impacted.

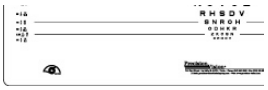
12.2.2 Visual Acuity

Visual acuity is a traditional measure of central visual function, particularly the ability of the eye to perceive details and is primarily cone-mediated. VA is the most common measure of visual function both in clinical practice as well as in clinical trials. Loss of acuity manifests as a decrease in the ability to perform detail-oriented tasks, such as reading and face recognition. In

the patient population with IRD due to biallelic *RPE65* mutations, VA is often severely impaired early in life.

In this clinical program, VA testing used high contrast charts with standardized letters of graded sizes to determine the smallest object seen at a specified distance. Early Treatment of Diabetic Retinopathy Study (ETDRS) VA test charts (Figure 40), the gold standard for VA measurements in clinical studies, were used for most subjects. For some young children, an analogous HOTV chart was used. HOTV charts include only the letters H, O, T and V, all of which center around a vertical axis and can be identified verbally by young children or shown to the test-taker on a matching HOTV card.

Figure 40: Example of ETDRS Visual Acuity Test Chart



Subjects were tested (using best correction [with optimal glasses/contact lens prescription] and well-illuminated charts) with each eye individually at three distances: 4 meters, 2 meters, and 0.5 meter. Visual acuity was determined based on the lowest lines (smallest letters) on which letters were correctly identified at each distance. The ETDRS chart includes letter sizes on each line following a geometric progression, such that VA can be converted to a visual angle score (LogMAR, or **Log**arithm of the **M**inimum **A**ngle of **R**esolution) allowing for comparison analyses, where *smaller* LogMAR values indicate *better* acuity (*i.e.*, less VA loss). For the VA analyses, a 0.1 change in LogMAR corresponds to a 5-letter (equivalent to one line) change on the ETDRS chart.

For subjects unable to correctly identify the largest line of letters on the chart, off chart VA measurements were collected (*i.e.*, counting fingers, hand motion perception, light perception, no light perception) and then were assigned a LogMAR value using the scale adapted from (Holladay 2004). This scale utilizes a 1-log-unit step between, for example, counting fingers and hand motion perception. Given this large step, this scale is conservative with respect to quantifying VA in assessment of safety, as it assigns worse (higher) acuity to off-chart VA than other scales. Based on recommendations from regulators and the Data Safety Monitoring Board overseeing the clinical program, a scale with a reduced 0.3-log-unit step between counting fingers and hand motion was used for sensitivity analyses beginning in 2013. This scale, adapted from Lange 2009, was recommended given concerns with overestimating any treatment effect (improvement or reduction in LogMAR) for subjects with off-chart vision measurements at

Baseline; this same scale is associated with Freiburg vision testing, or FrACT, though this testing method itself (developed by Professor Michael Bach [senior author on the Lange *et al.*, 2009 publication] and colleagues for patients with very low vision) was not used in the clinical program.

12.2.3 Visual Field

Visual field refers to the area in which objects can be detected in the periphery of the visual environment, while the eye is focused on a central point. Visual field loss (*i.e.*, decreased peripheral vision or increased "tunnel vision"), manifests in an inability to detect peripheral objects and, often, in a reduced ability to avoid obstacles. Visual fields can be measured by using kinetic and/or static techniques with instruments that are operated either manually or automatically (computerized). All methods include an apparatus where a patient is seated with his/her chin in a chin rest, looking at a dome-shaped screen, and asked to focus the eye being tested on a central point while the contralateral eye is patched. Kinetic perimetry involves moving the test object from the non-seeing (*i.e.*, far periphery) to the seeing area (with the brightness of the test stimulus held constant) and mapping the boundary where the test stimulus is first detected. Threshold static automated perimetry measures the relative intensity thresholds (levels of brightness) of individual points in the visual field; the size and location of the target is kept constant and the brightness is varied until a threshold level is identified for each test location. In the Phase 3 clinical trial, kinetic fields were measured with manual Goldmann perimetry (assessing the full extent of the visual field for each eye) and static fields were measured using Humphrey computerized testing (evaluating the sensitivity of specific points in the central retina [macula and fovea]).

Each test has benefits and drawbacks. Goldmann VF testing is frequently used in low vision patients and those with nystagmus since patient fixation can be monitored by the technician (perimetrist) conducting the test. Additionally, Goldmann perimetry is better at identifying islands of visual field and/or scotomas (isolated areas of inability to see) in the periphery. Computerized visual fields such as Humphrey, on the other hand, are beneficial because they are automated and based on computerized algorithms. The results are presented quantitatively and can be monitored over time as the algorithm automatically compares each subject's result to age-matched normative data. The Humphrey analyzer is also more sensitive to slight changes in the central field (field corresponding to the macula and fovea).

12.2.3.1 Goldmann Visual Field

Goldmann kinetic perimetry testing employs a dome-shaped white screen positioned a set distance in front of the patient, with the patient's head positioned in a chin rest. Each eye is tested individually with the contralateral eye patched. The patient focuses the eye being tested on a central point on the screen and a target light is projected on the screen as a visual stimulus. The technician (perimetrist) manually moves the light from the far periphery centrally into the patient's visual field. The patient indicates when the light is detected by pressing a button. The test is conducted using different sizes and different intensities of target light stimuli.

The technician records the patient's responses on a standardized graphic display form representing visual space. Contour lines (isopters) are drawn for each stimulus outlining the

boundaries of the visual field. In the Phase 3 study, Goldmann VFs were reported as sum total degrees that the subject was able to perceive across all 24 meridians. The extent of VF was measured along each of the 24 meridians from the central fixation point to the boundary (*i.e.*, point of the isopter intersection) of the detected visual field, and then a summation of the measure from each of the 24 meridian measurements represents the sum total degrees for that eye. Higher sum total degrees indicate a greater area of functional and light sensitive retina, corresponding to a greater field of vision for the tested eye. Using this approach, the maximal visual field is approximately 1200 to1400 sum total degrees in individuals without visual impairment. In clinical practice, Goldmann VFs are usually assessed qualitatively, with a subjective evaluation of changes in shape, size, and area of the fields over time (Figure 41). The use of sum total degrees allows for a quantitative assessment and provides a numeric estimate of the entire field, which can be analyzed over time.

Figure 41: Visual Field Meridians and Standard Isopters on the Goldmann Perimeter for the Right Eye of a Normal 43-Year-Old Patient

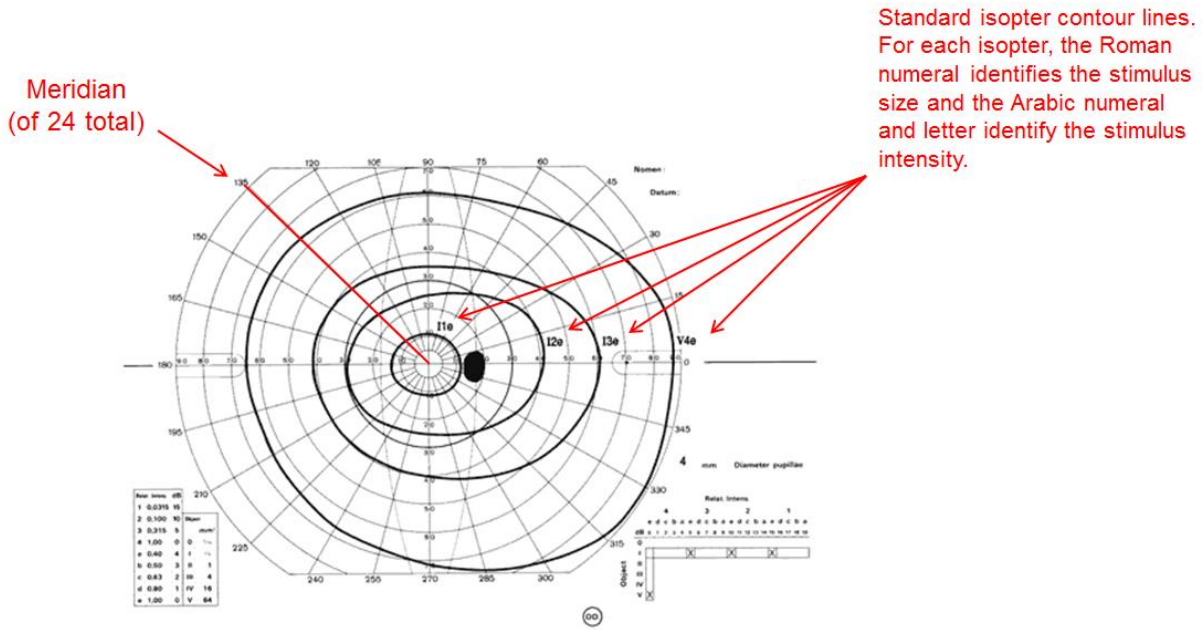
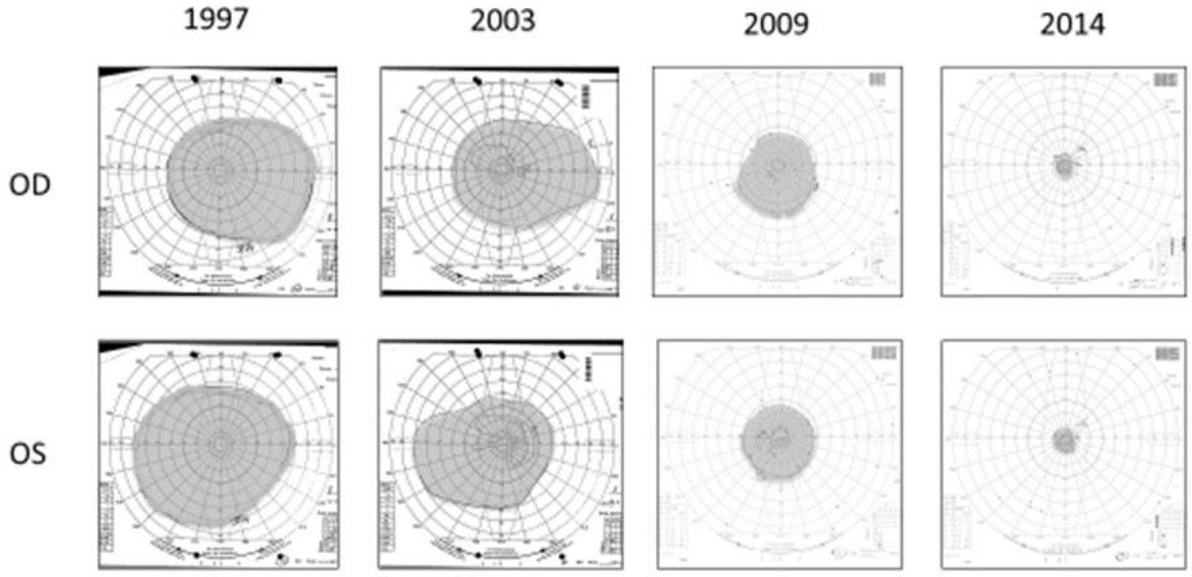


Figure 42: Change in Goldmann Visual Field (V4e stimulus) over time in a Representative Subject from the *RPE65* Natural History Study



OD = oculus dextrus (right eye); OS = oculus sinister (left eye).
Subject age: 1997, 6 years; 2003, 12 years; 2009, 18 years; 2014, 23 years.

In the Phase 3 study, two different target light sizes, III4e and V4e, were used for Goldmann VF testing. The V4e target is the largest target (64 mm^2 in area, ~9 mm diameter) used for Goldmann testing, and the III4e target is $1/16^{th}$ smaller in total area and $1/4^{th}$ the diameter of the V4e target. Both the III4e and V4e targets use the brightest possible light intensity. The V4e stimulus, as the biggest and brightest available on the Goldmann perimeter, is used to detect the lower limit of field in poorly sighted individuals. The III4e stimulus is used in visual disability determinations and therefore provides a reference for traditional measures of visual impairment *e.g.*, legal blindness.

Each subject was to be tested with both the III4e and V4e test stimulus in each eye at Baseline. This result was used to identify which test stimulus to use for follow-up visits. If the subject could see and reliably perform testing using the III4e test stimulus at Baseline, this target size was to be used for each subsequent visit. If the subject was unable to identify the III4e test stimulus at Baseline, the V4e test stimulus was to be used for each subsequent visit.

12.2.3.2 Humphrey Visual Field

The Humphrey Visual VF Analyzer is an automated (*i.e.*, computerized) system using a stationary stimulus to measure the sensitivity of points within the central visual field. Similar to the Goldmann perimetry, subjects sit in front of a dome-shaped white screen, with their head stabilized in a chin rest, with the test eye focused on a central target; each eye is tested individually, with the contralateral eye patched, and the subject indicates via a button when a target light is detected. Target sizes of stimuli frequently use the same convention as Goldmann (*i.e.*, I through V). In threshold testing, an attempt is made to measure the intensity of the

dimmest stimulus which can be detected 50% of the time at a given location. The approach used in the Phase 3 study included a size V target (same size as the V4e test stimulus used in Goldmann perimetry) shown in predefined spots within the central 4 degrees of visual field. The light flashes vary in intensity in order to determine a threshold at each location. An algorithm determines the pattern of flashes and presents a readout following the test. A computerized testing program called "FastPac" was selected, as it is the fastest test available on the Humphrey analyzer. Longer tests are challenging, particularly for pediatric subjects and those with nystagmus.

Two assessments were recorded for each eye at each study visit from the Humphrey analyzer: foveal sensitivity and mean macula thresholds. Foveal sensitivity measures the function of the fovea, the very center cone-rich area of the macular region of the retina, where visual acuity is the highest. This foveal threshold, reported in decibels (dB), is measured directly by the analyzer. In contrast, the mean macula threshold (also reported in dB) is calculated by deriving the mean of 16 points tested within the central 4 degrees of vision (corresponding anatomically to the macular area of the retina). Each of these 16 points indicates the intensity of the stimulus seen 50% of the time at that location. For both HVF threshold assessments (foveal sensitivity and mean macular threshold), the higher the dB, the more sensitive (or better) is the vision is at that location.

12.2.4 Visual Function Questionnaire

The visual function questionnaire is a patient-reported outcome (PRO) evaluating the activities of daily living that are dependent on vision, or those which have a visual component. The questionnaire was developed to accommodate individuals with extremely poor vision. The questionnaire consists of 25 questions with scaled numerical answers from 0 to 10 where lower scores correspond to greater vision loss. Subjects were asked to provide responses regarding the perceived degree of difficulty (on the 0 to 10 scale) of various activities of daily living over the previous month. For example, one question asked, "In unfamiliar surroundings, how often do you run into things by mistake (*e.g.*, stub your toe, hit your shoulder, trip)?". Respondents had to choose a number on a 0 to 10 scale where 0 = always and 10 = never. Modifications were made to assist young subjects by providing age-appropriate "multiple-choice" options to correspond with the scaled numbers. The average of all numerical responses was reported as the final score. The parents or guardians of children under 18 also completed the questionnaire and the scores were followed individually (*i.e.*, the final subject scores and parent/guardian scores were not averaged) over time. Increases in the mean score over time indicate a reduction in the perceived difficulty with daily living activities and potentially improvements in functional vision, *i.e.*, carrying out activities of daily living that are dependent on vision, or have a visual component.

12.2.5 Community-based Functional Vision (or Orientation and Mobility) Assessments

During the clinical development program for voretigene neparvovec, a 'real-world' or community-based functional vision assessment was developed to be utilized in the Phase 3 study. Community-based (at home and the surrounding environments) functional vision assessments (also referred to as orientation and mobility [O&M] assessments) were conducted by trained low vision therapists at baseline and at one and two-year follow-up during the Phase 3 study.

Specialists were independent from both the Sponsor and the clinical study teams and masked to treatment assignment. Assessments were conducted in the subject's home environment and surrounding area, and the same evaluator performed all assessments on a given subject. Narratives summarized the functional vision findings, and the assessments included specific questions and tasks that enabled the evaluator to determine various visual abilities within the areas of basic visual skills, illumination, O&M observed tasks, mobility, and observed tasks related to activities of daily living (ADL).

By design, such functional vision assessments are structured, but not rigidly standardized, primarily subjective in nature, and highly individualized. The purpose of this type of functional assessment is to observe the subject in the comfort and familiarity of their home and community, undertaking tasks that they are accustomed to performing; this allows the assessor to gather performance information that can be used to paint a picture of what an individual experiences on a daily basis with real world activities.

12.2.6 Contrast Sensitivity

While visual acuity testing uses only black and white letters (high contrast), the real world consists of shades of gray. Low contrast environmental conditions (e.g., fog, glare) are encountered frequently. Contrast sensitivity (CS) testing examines the ability to see objects of different saturations (shades of gray). Contrast sensitivity was measured for each eye individually using two different Pelli-Robson Contrast Sensitivity Charts (Figure 43) to determine the lowest contrast at which letters could be seen. This chart includes letters that are all the same size and are arranged into triplets of the same contrast. There are two triplets of decreasing contrast per line. The chart was lit to assess photopic vision, or vision in daylight or other bright light, believed to primarily involve function of the cones of the retina. Contrast sensitivity of the eye being tested is determined by the faintest triplet for which 2 of the 3 letters were read correctly. The log contrast sensitivity for each triplet is indicated on the scoring sheet with larger numbers indicating greater contrast sensitivity. Contrast sensitivity was not performed in young subjects unable to read letters due to their age.

Figure 43: Example of Pelli-Robson Contrast Sensitivity Chart

12.2.7 Pupillometry

Pupillometry is an objective, physiological test of retinal function in which the pupil diameter is measured before and after the eyes are stimulated with light. Pupillometry can be used to assess changes in retinal function because pupillary responses depend on the signal from the retina having detected a light stimulus relayed to the brain via the optic nerve and back to the iris sphincter muscles of the eye. Pupillary light reflex (PLR) testing (i.e., pupillometry) was performed after 40 minutes of dark adaptation. Subjects placed their forehead against a machine (the Procyon pupillometer) where infrared cameras recorded both pupils continuously and simultaneously. During the test period, sequences of light flashes were delivered alternatively between the two eyes from the dimmest to the brightest illumination. Additional neutral density (ND) filters were added to the dimmest level to decrease the light intensity further. Light stimuli were short (0.2 seconds) and spaced at approximately 3-second intervals. A minimum of 12 tests were recorded at Baseline to measure the constriction of each pupil at increasing light levels. The degree of pupil construction at each light level was monitored in each eye over time.

12.2.8 Optical Coherence Tomography

Optical coherence tomography is an imaging technology similar to ultrasound, however utilizing light waves, for non-invasive imaging of ocular structures. OCT captures cross sectional images of the retinas, delineating the different retinal layers. The resolution of OCT images is much better than ultrasound enabling precise measurements of the thickness of the central retina (fovea) and the total macular volume. Additionally, high resolution OCTs can be used to identify the presence of fluid in the subretinal or intraretinal space. In the Phase 3 study, OCT was included primarily as a safety measure to monitor for retinal atrophy or severe thinning potentially due to disease progression, the administration procedure and/or the vector. Thickness measurements on OCT also served as an inclusion criterion in this clinical program to estimate whether sufficient viable retinal cells were present for investigational product administration. Based on the hypothesized mechanism of action, the presence of sufficient viable retinal cells is considered necessary for therapeutic efficacy as well as surgical safety. OCT was also used to monitor for retinal surgical changes, including holes and tears, in subjects following intervention.

For the Phase 3 study, the Heidelberg Spectralis Spectral Domain OCT was the preferred OCT system. However, nystagmus (abnormal involuntary rapid eye movements), which is commonly present in patients with IRD due to biallelic *RPE65* mutations, can interfere with adequate image capture on the Spectralis machine. If a study subject had nystagmus, an alternate OCT system, the Zeiss Stratus OCT, was used to measure thickness and volume.

12.2.9 Fundus Photography

Fundus photography captures images of the posterior segment of the eye, including the retina, optic nerve, and vitreous. In the clinical program, fundus photography was included as a safety assessment. The subjects' eyes were dilated and then photographed individually to capture overlapping images of both the central and peripheral retina (*i.e.,* the macula as well as the superior, inferior, nasal and temporal periphery). The photographs were analyzed for remaining healthy areas of the macula, with the areas not affected by atrophy or degeneration measured in relation to the size of the optic nerve head border, or disc area. Areas of atrophy or degeneration may be evidenced on fundus photography by pigmentary loss, migration or other disturbance.

12.2.10 Summary

In order to assess functional vision/visual function and safety in this study, the clinical deficits associated with *RPE65* mutation-associated retinal dystrophy (*e.g.*, nyctalopia) were taken into consideration to select appropriate, clinically meaningful endpoints (Table 36).

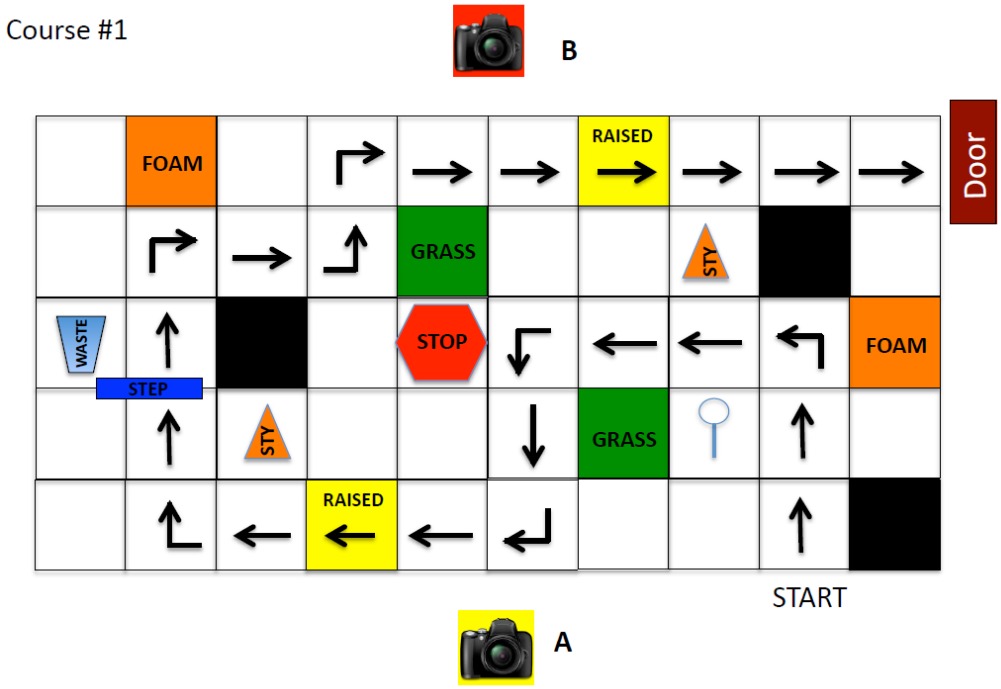
Table 36: Phase 3 Ophthalmic Endpoints

Endpoint	Units of measure	Interpretation
MLMT	Score Change	Positive score change signifies passing at a lower light level (*i.e.*, improved ability to navigate under a range of different lighting conditions)
FST	Relative unit (dB) converted to absolute unit (cd.s/m^2) to allow comparison across sites/subjects. The analysis uses log10(cd.s/$m^{2)}$	For log10(cd.s/m^2), a more negative value signifies a lower threshold, corresponding to improved sensitivity to light (*i.e.*, improved photoreceptor function)
VA	LogMAR	A lower LogMAR signifies better visual acuity (improved VA, less VA loss) [LogMAR 1.0 = 20/200 Snellen LogMAR 0 = 20/20 Snellen 0.1 LogMAR = 5 ETDRS letters; equivalent to one line]
GVF	Sum total degrees	Higher sum total degrees signify a larger field of vision (improved GVF)
HVF	dB	Higher dB signifies increased sensitivity (improved HVF)
CS	logContrast Sensitivity (scored by faintest triplet from which 2 out of 3 letters identified correctly)	Larger log CS numbers signifies CS is high (i.e., letters of lower contrast can be read correctly, improved CS)
Visual Function Questionnaire	Summation of points for all questions	A higher score signifies that visually-dependent tasks are perceived to be less difficult (i.e., improved functional vision)
Community- Based Functional Vision (O&M)assessments	Subjective narrative summary	Descriptive report
PLR	Constriction amplitude (area under the curve [AUC])	Higher amplitude and/or velocity of constriction signifies better retinal function [typically evaluated qualitatively] AUC analyses: Higher AUC signifies greater amplitude of constriction (increased PLR)
OCT	Microns	Larger numbers signify thicker structure
Fundus Photography	Range of disc area	Larger numbers signify increased area of healthy retina *without* confluent atrophy

ADL = activities of daily living; AUC = area under the curve; CS = contrast sensitivity; dB = decibel; ETDRS = Early Treatment of Diabetic Retinopathy Study; FST = full-field light sensitivity threshold; GVF = Goldmann visual field; HVF = Humphrey visual field; log10(cd.s/m^2) = logarithm of candela second per meter squared; LogMAR = logarithm of the minimum angle of resolution; MLMT = multi-luminance mobility testing; N/A = not applicable; OCT = optical coherence tomography; O&M = orientation and mobility; PLR = pupillary light reflex; VA = visual acuity; VF = visual fields.

In aggregate, the visual assessments conducted in the Phase 3 study for efficacy and safety provide a comprehensive and meaningful overview of total visual capacity, overall subject performance, and are appropriate for patients with biallelic *RPE65* mutations.

12.3 MLMT Courses



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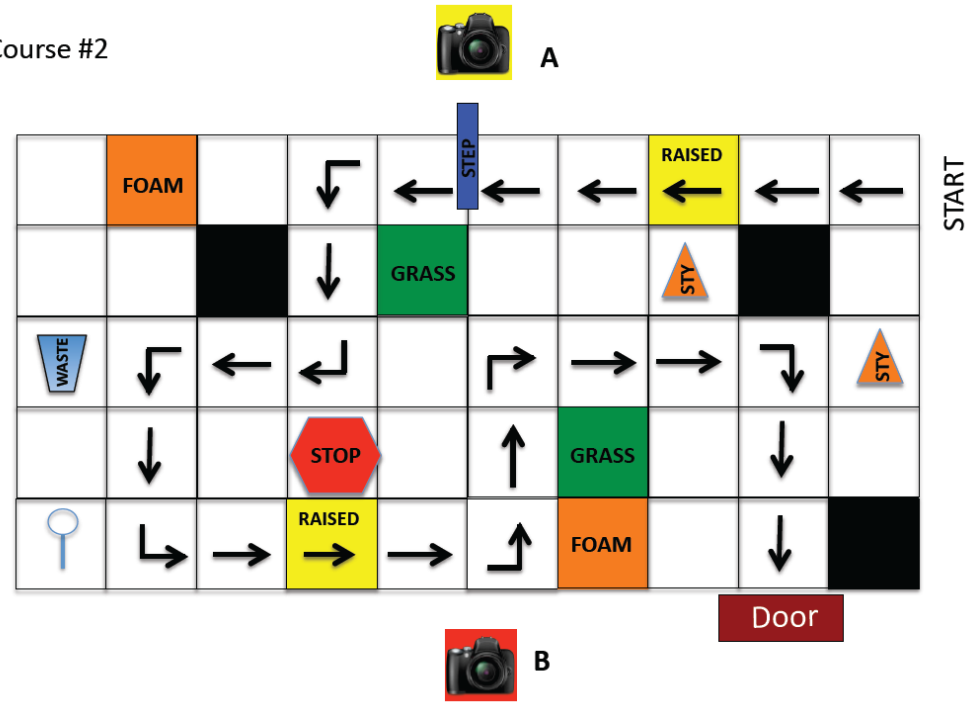

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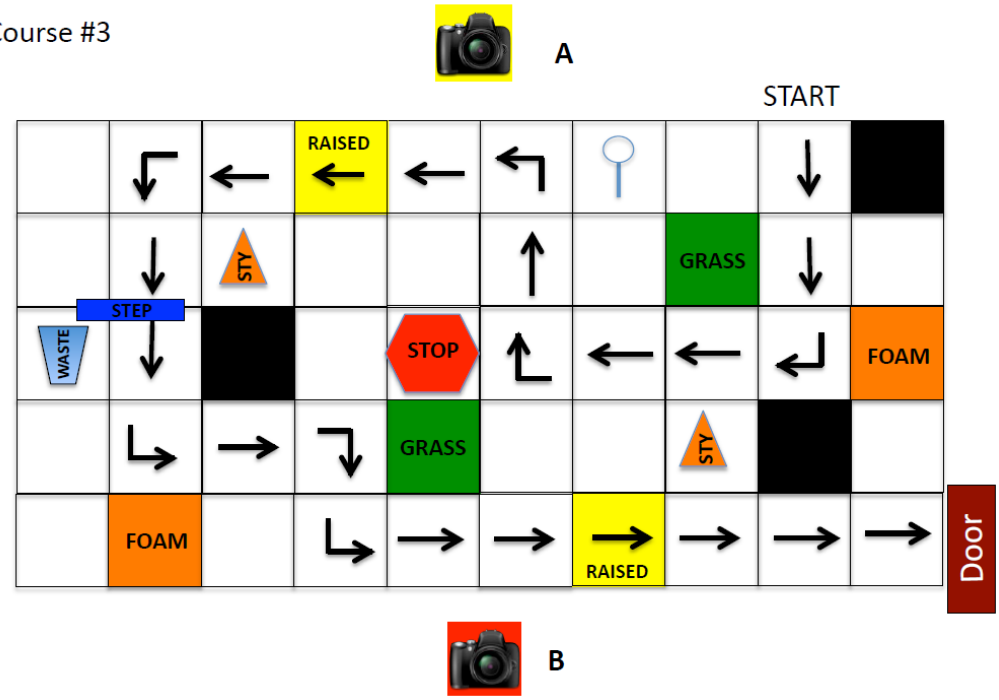

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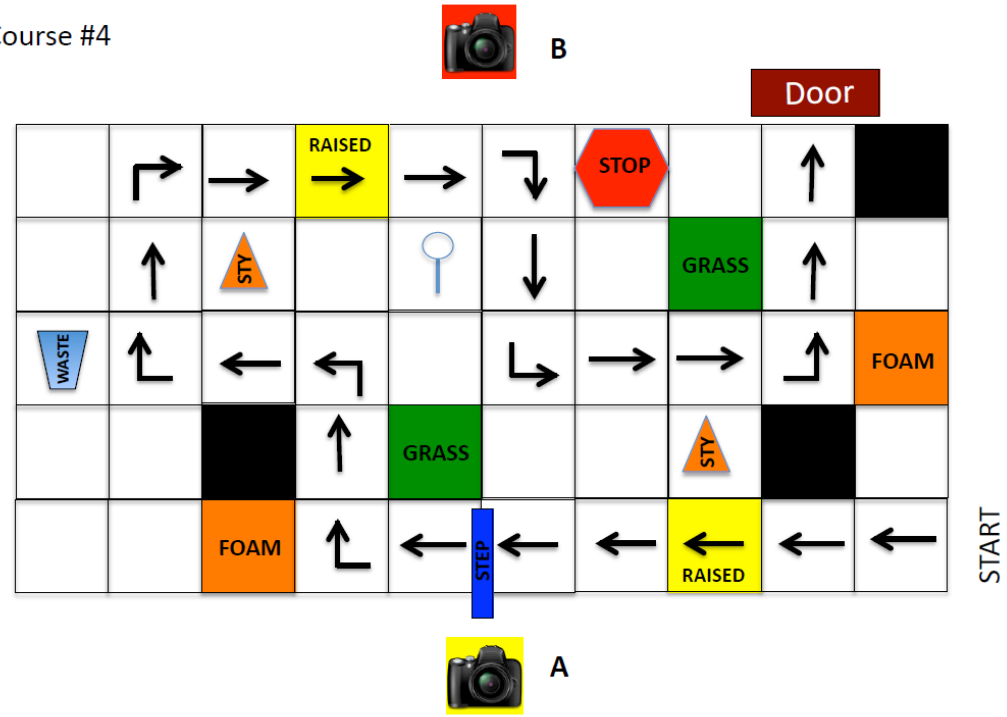

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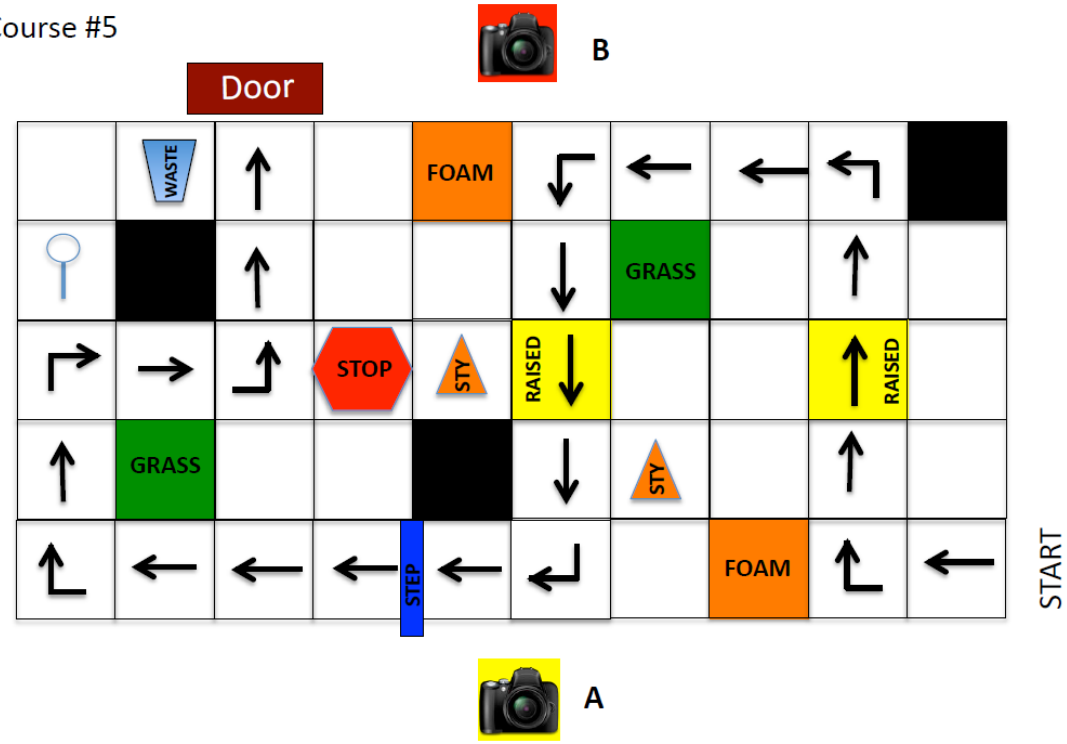

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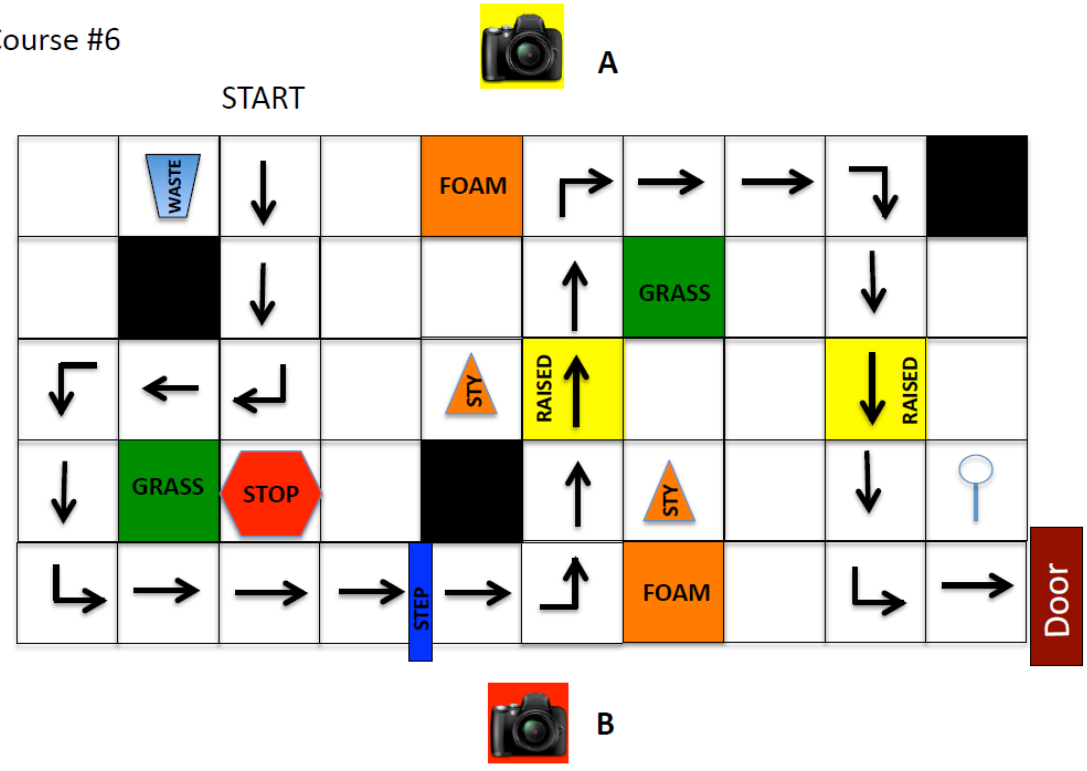

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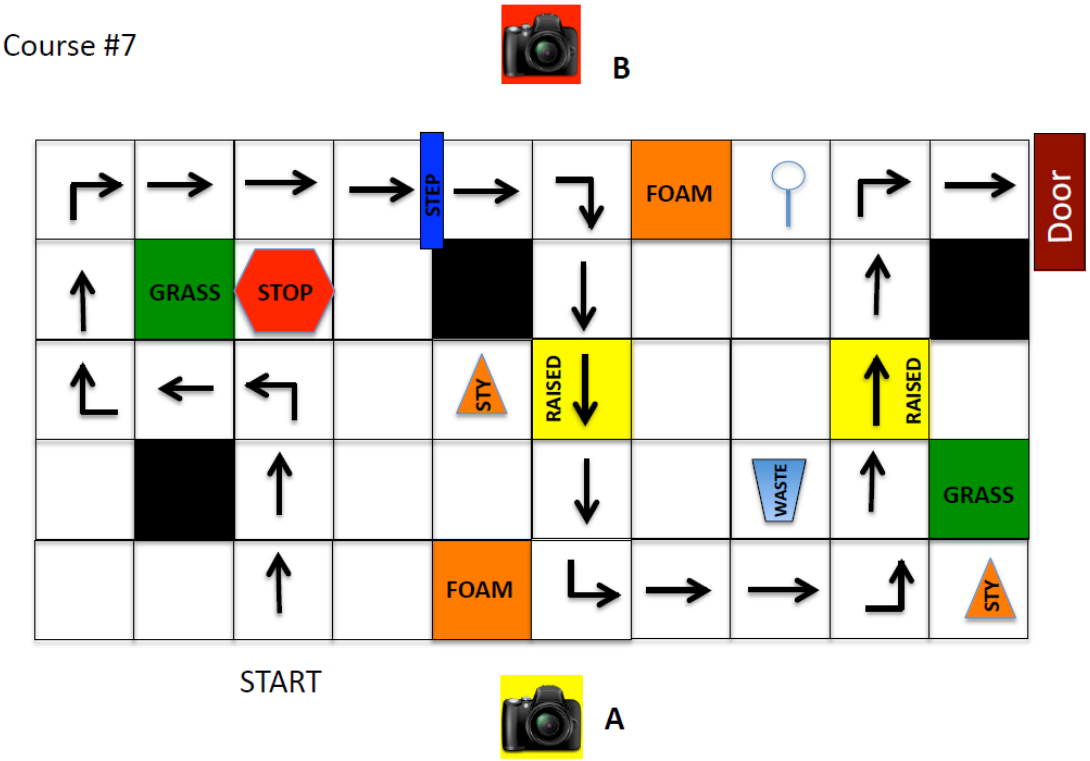

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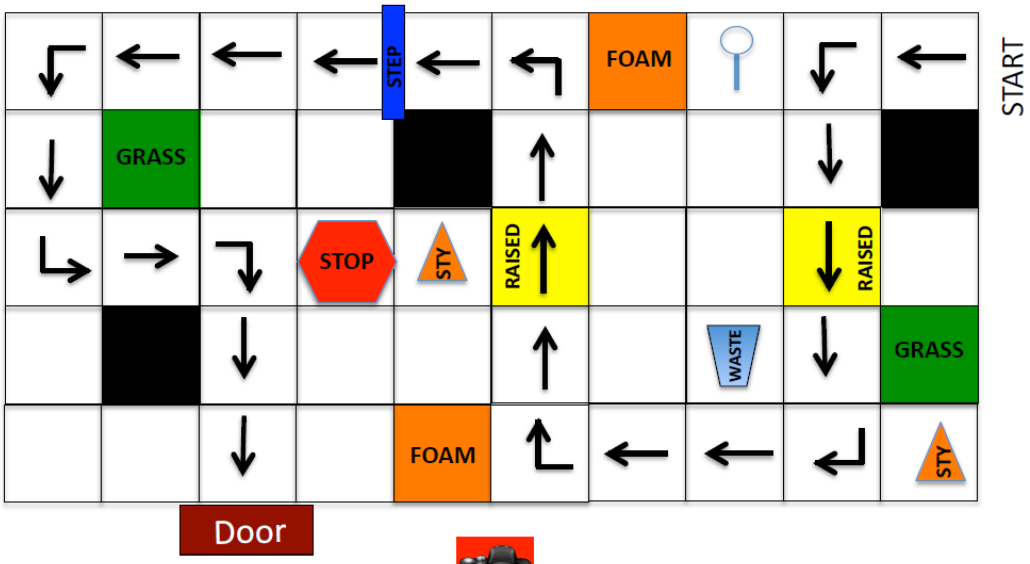

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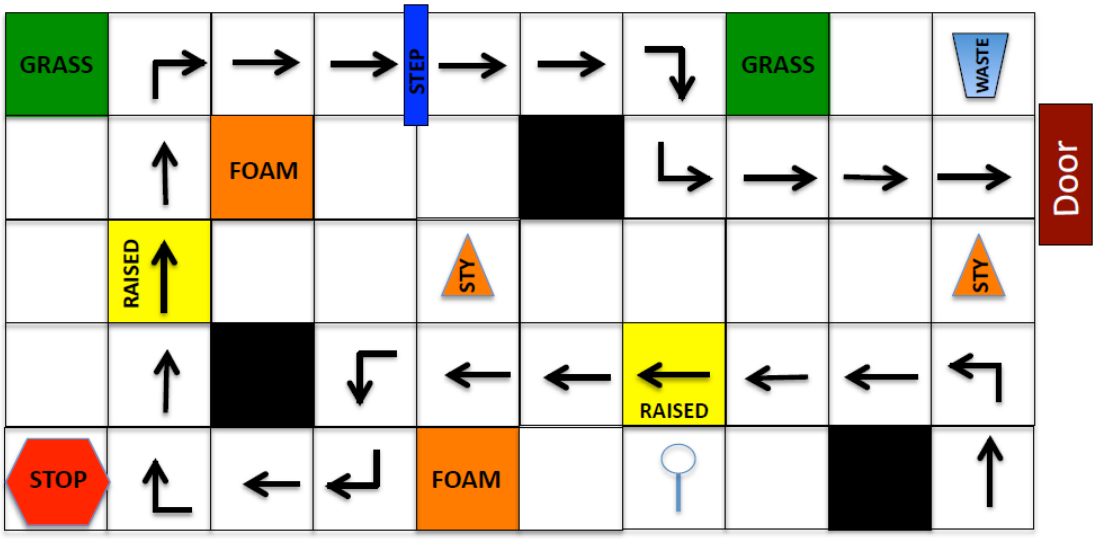

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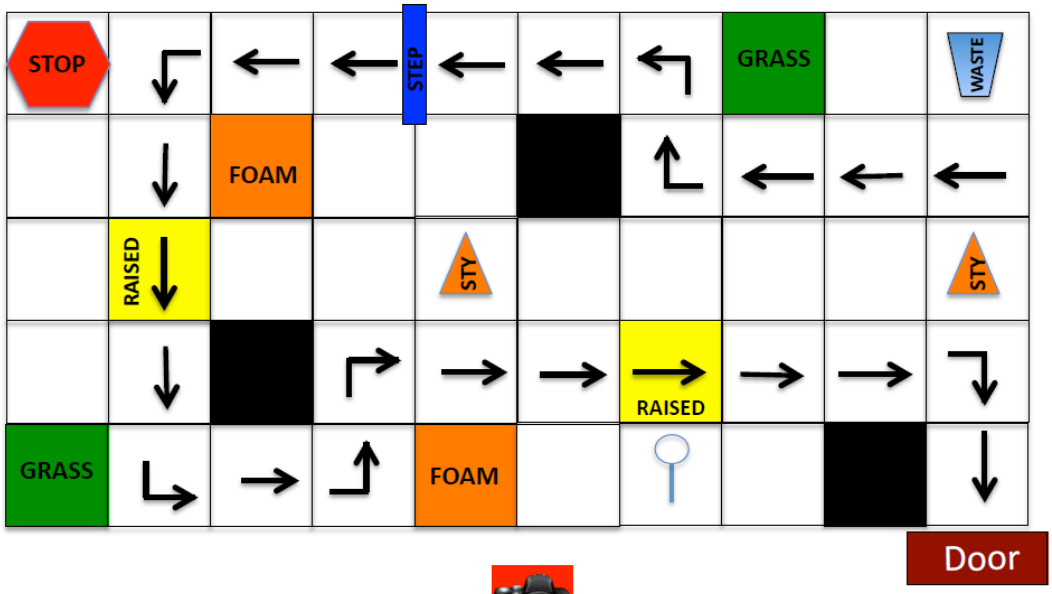

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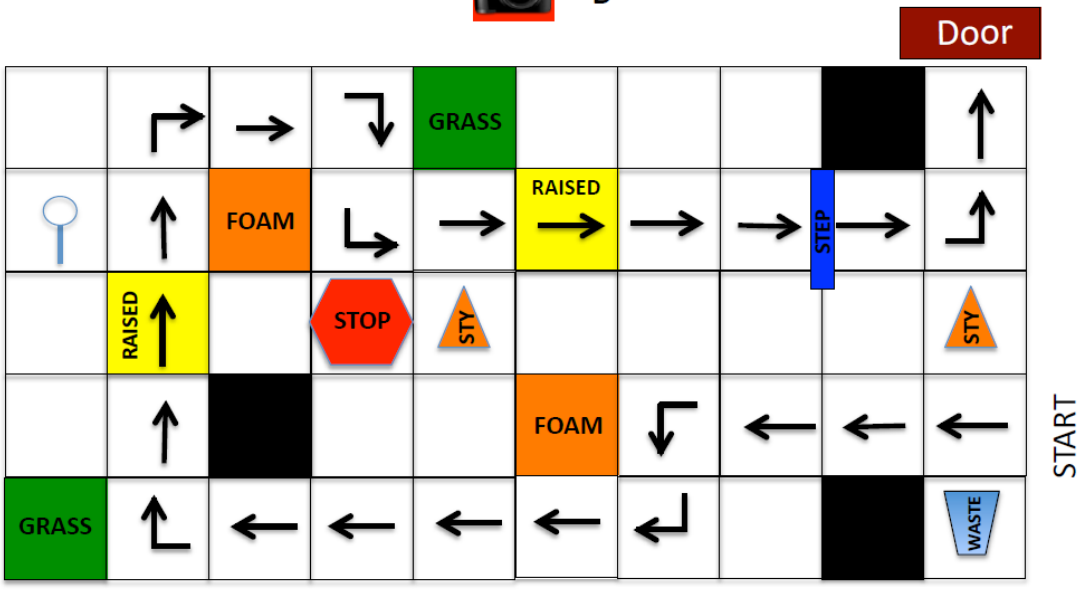

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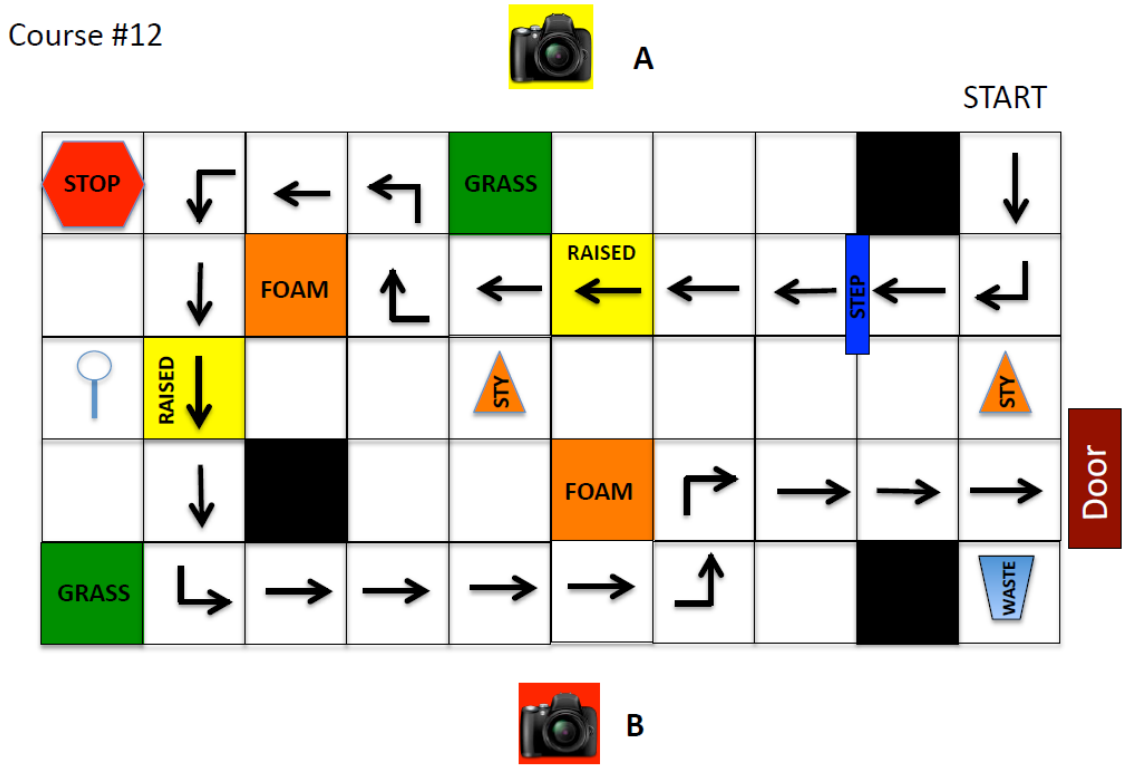

12.4 Inclusion and Exclusion Criteria in the Natural History Study

Inclusion Criteria

Subjects (medical records) had to meet the following inclusion criteria to be eligible for participation in the study:

a. Males or females born between January 1, 1963 and December 31, 2010 (inclusive)

b. Genetic diagnosis consistent with autosomal recessive mutation(s) in the *RPE65* gene

c. Minimum of two office visits/clinic encounters occurring prior to the following:

a) Retinal surgery or surgery that penetrated the posterior chamber (*e.g.*, vitrectomy, trabeculectomy, glaucoma filtering surgery, and retinal device implantation)

b) Enrollment in an interventional study for inherited retinal degenerations (*i.e.*, surgical, device, and/or study drug interventional studies).

Exclusion Criteria

Subjects (medical records) were not to be excluded based on their gender, race, or ethnicity.

Subjects (medical records) must have met none of the following exclusion criteria to be eligible for participation in the study:

1. Other retinal disorders or other known retina-specific mutations
2. Other eye disorders that impact retinal function (*e.g.* glaucoma)
3. Systemic disease associated with mutations in other retinal genes, such as known central nervous system, auditory, or renal problems
4. Only one office visit/clinic encounter

12.5 Schedule of Assessments in Study 301

Assessment	Screening Visit	Baseline Visit	Day -3A[1]	Day								Year 1B/C
				0A/B	1A/B	3A/B	8B[1]	14B	30B/C	90B/C	180B/C	
Vision and medical history, prior medications	X											
Physical Exam		X										X
Pregnancy test (if applicable)	X			X								
Begin prednisone			X									
Discontinue prednisone							X					
Vital signs		X		X	X	X		X				X
Hematology		X		X	X	X		X	X	X		X
Chemistry		X		X	X	X		X	X	X		X
Urinalysis		X		X	X	X		X	X	X		X
Virology	X											
PBMC collection		X							X	X		X
AAV Ab		X							X	X		X
Peripheral blood/tear PCR		X		X	X	X		X	X	X	X[2]	X
Ophthalmic exam	X[3]	X[3]			X	X		X	X[3]	X[3]	X[3]	X[3]
Mobility testing	X	X							X	X	X	X
Pupillometry		X							X	X	X	X
Visual acuity tests	X	X			X[4]	X[4]		X[4]	X	X	X	X
Visual field tests	X	X							X	X	X	X
Orientation and mobility assessment		X										X
Visual function questionnaire		X							X	X	X	X
Full-field light sensitivity threshold testing		X							X	X	X	X
Contrast sensitivity		X							X	X	X	X
AE recording		X		X	X	X		X	X	X	X	X
Concomitant medication recording		X		X	X	X		X	X	X	X	X

1 Days -3A and 8B were not study visits. Subjects were to begin taking systemic corticosteroids prescribed following confirmation of eligibility and randomization or crossover to the Intervention group.
2 Tear collection only.
3 Ophthalmic exams at these visits were to include OCT and fundus photography.
4 Ophthalmic exams at these visits were to include visual acuity testing to monitor recovery from surgery.

12.6 Study 301 Inclusion and Exclusion Criteria

Inclusion Criteria

Male and female subjects of any ethnic group were eligible for participation in this study, providing they met the following criteria:

1. Willingness to adhere to protocol and LTFU as evidenced by written informed consent or parental permission and subject assent (where applicable).
2. Diagnosis of LCA due to *RPE65* mutations; molecular diagnosis is to be performed, or confirmed, by a CLIA-certified laboratory.
3. Age three years old or older.
4. Visual acuity worse than 20/60 (both eyes) and/or visual field less than 20^{o} in any meridian as measured by III4e isopter or equivalent (both eyes).
5. Sufficient viable retinal cells as determined by non-invasive means, such as OCT and/or ophthalmoscopy. Must have either: *1)* an area of retina within the posterior pole of > 100 µm thickness shown on OCT; *2)* ≥ 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole; or *3)* remaining visual field within 30^{o} of fixation as measured by III4e isopter or equivalent.
6. Subjects must be evaluable on mobility testing (the primary efficacy endpoint) to be eligible for the study. Evaluable is defined as:
    a. The ability to perform mobility testing within the luminance range evaluated in the study. Individuals must receive an accuracy score of ≤ 1 during Screening mobility testing at 400 lux or less to be eligible; individuals with an accuracy score of > 1 on all Screening mobility test runs at 400 lux, or those who refuse to perform mobility testing at Screening, will be excluded.
    b. The inability to pass mobility testing at 1 lux. Individuals must fail Screening mobility testing at 1 lux to be eligible; individuals that pass one or more Screening mobility test runs at 1 lux will be excluded.

Exclusion Criteria

Subjects who met any of the following conditions were excluded from this study:

1. Unable or unwilling to meet requirements of the study, including receiving bilateral subretinal vector administrations.
2. Any prior participation in a study in which a gene therapy vector was administered.
3. Participation in a clinical study with an investigational drug in the past six months.
4. Use of retinoid compounds or precursors that could potentially interact with the biochemical activity of the RPE65 enzyme; individuals who discontinue use of these compounds for 18 months may become eligible.
5. Prior intraocular surgery within six months.
6. Known sensitivity to medications planned for use in the peri-operative period.
7. Pre-existing eye conditions or complicating systemic diseases that would preclude the planned surgery or interfere with the interpretation of study. Complicating systemic diseases would include those in which the disease itself, or the treatment for the disease, can alter ocular function. Examples are malignancies whose treatment could affect central

nervous system function (for example: radiation treatment of the orbit; leukemia with CNS/optic nerve involvement). Subjects with diabetes or sickle cell disease would be excluded if they had any manifestation of advanced retinopathy (*e.g.*, macular edema or proliferative changes). Also excluded would be subjects with immunodeficiency (acquired or congenital) as there could be susceptibility to opportunistic infection (such as CMV retinitis).

8. Individuals of childbearing potential who are pregnant or unwilling to use effective contraception for four months following vector administration.
9. Individuals incapable of performing mobility testing (the primary efficacy endpoint) for reason other than poor vision, including physical and attentional limitations.
10. Any other condition that would not allow the potential subject to complete follow-up examinations during the course of the study or, in the opinion of the investigator, makes the potential subject unsuitable for the study.

Subjects who did not meet all of the enrollment criteria were not to be enrolled. Any violations of these criteria must have been reported in accordance with Spark Therapeutics and local ethics committees' policies and procedures.