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Applicant	Spark Therapeutics, Inc.
Established Name	AAV2-hRPE65v2, voretigene neparvovec
(Proposed) Trade Name	LUXTURNA
Pharmacologic Class	Adeno-associated viral type 2 (AAV2) gene therapy vector
Formulation(s), including Adjuvants, etc	Concentrate for solution
Dosage Form(s) and Route(s) of Administration	Single subretinal injection
Dosing Regimen	$1.5 \times 10^{11}$ vector genomes in total volume of 0.3 mL per eye
Indication(s) and Intended Population(s)	Treatment of patients with vision loss due to confirmed biallelic <i>RPE65</i> mutation-associated retinal dystrophy

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## GLOSSARY

AAV	Adeno-associated viral
AC	Advisory committee
AE	Adverse event
BLA	Biologics license application
C $\beta$ A	Chicken beta actin
CHOP	Children's Hospital of Philadelphia
CI	Confidence Interval
CMC	Chemistry, Manufacturing and Controls
CMV	Cytomegalovirus
CSR	Clinical study report
DSMB	Data and Safety Monitoring Board
ICF	Informed consent form
ITT	Intent-to-treat
LCA	Leber congenital amaurosis
LogMAR	Logarithm of the minimum angle of resolution
LTFU	Long-term follow-up
MLMT	Multi-luminance mobility testing
OCT	Optical coherence tomography
PP	Per protocol
RP	Retinitis pigmentosa
RPE	Retinal pigment epithelium
SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse event

## 1. EXECUTIVE SUMMARY

Voretigene neparvovec is a gene therapy product. It is an adeno-associated viral (AAV) type 2 vector with the cytomegalovirus (CMV) enhancer and the chicken beta actin (C $\beta$ A) promoter driving expression of human retinal pigment epithelial 65 (*RPE65*) kilodalton protein. This original Biologics License Application (BLA) seeks licensure of voretigene neparvovec for treating patients with vision loss due to confirmed biallelic *RPE65* mutation-associated retinal dystrophy, which affects 1,000-2,000 patients in the US.

Three clinical trials (Study 301, 101 and 102) were submitted to the FDA. Study 301 was the pivotal study and served as the primary evidence of safety and efficacy to support this original BLA for voretigene neparvovec. Both Study 101 and Study 102 were Phase I studies, and they were included to provide supportive evidence for safety evaluations.

Study 301 was a Phase 3, open-label, randomized, and controlled trial conducted under IND 13408 in two US study sites. A total of 31 subjects (21 subjects in the treatment group and 10 subjects in the control group) were randomized in the study, ranging in age from 4 to 44 years old. The primary efficacy endpoint was change in performance on the multi-luminance mobility testing (MLMT) using both eyes from baseline to one year following vector administration. The median one-year MLMT score change in the intent-to-treat (ITT) analysis set was 2 for the treatment group and 0 for the control group, a statistically significant difference based on a Wilcoxon Rank-Sum test using an exact method (p-value = 0.001) as well as a permutation test (p-value = 0.001). Further analysis showed that 11 subjects (11/21, 52%) in the treatment group had an MLMT score change of 2 or more, while only one subject (1/10, 10%) in the control group had an MLMT score change of at least 2. Similar analyses for the MLMT score change using both eyes based on modified intent-to-treat (mITT) and per protocol (PP) analysis sets revealed consistent results in favor of the treatment group.

Results for the secondary efficacy endpoints in Study 301 were consistent with those for the primary efficacy endpoint. The analysis of the full-field light sensitivity threshold (FST) using both eyes showed a mean (SE) change from baseline to one year of -2.08 (0.29) log<sub>10</sub>(cd.s/m<sup>2</sup>) for the treatment group and 0.04 (0.44) log<sub>10</sub>(cd.s/m<sup>2</sup>) for the control group based on a longitudinal repeated measures model. The treatment difference (95% CI) between two groups of -2.11 (-3.19, -1.04) log<sub>10</sub>(cd.s/m<sup>2</sup>) was statistically significant (p < 0.001).

The median MLMT score change at one year compared to baseline using first-treated eye was 2 for the treatment group and 0 for the control group. The MLMT score change was statistically significantly different between two study groups based on a Wilcoxon Rank-Sum test using an exact method (p-value = 0.003) as well as a permutation test (p-value = 0.001). Fifteen (15) subjects (15/21, 71%) in the treatment group had an MLMT score change of 2 or more, whereas no subject in the control group (0/10) showed an MLMT score change of at least 2 using respective control eyes.

A longitudinal repeated measures analysis of visual acuity (VA) averaged over both eyes showed a mean (SE) change from baseline to one year of -0.16 (0.07) logarithm of the minimum angle of resolution (LogMAR) for the treatment group and 0.01 (0.10) LogMAR for the control group, resulting in a mean (95% CI) treatment-effect difference of -0.16 (-0.41, 0.08). Though the difference is not statistically significant ( $p = 0.17$ ), it is numerically in favor of voretigene neparvovec treatment.

Among 20 subjects (40 treated eyes) treated with voretigene neparvovec in Study 301, 12 subjects (21 treated eyes) had ocular adverse events (AEs); these were primarily related to the administration procedure. Most ocular AEs were resolved with minimal or no intervention and without sequelae. Two (10%) subjects in the treatment group experienced three serious adverse events (SAEs) at time points distant from vector administration. All SAEs were considered unlikely to be related to study product or study product administration procedure. No deaths occurred.

The efficacy results of Study 301 provided statistical evidence to support the proposed indication that administration of voretigene neparvovec improves the ability to navigate a course with obstacles (as measured by MLMT) in patients with vision loss due to confirmed biallelic *RPE65* mutation-associated retinal dystrophy.

## 2. CLINICAL AND REGULATORY BACKGROUND

### 2.1 Disease or Health-Related Condition(s) Studied

Hereditary retinal dystrophies are a broad group of genetic retinal disorders that are caused by mutations in any one of over 220 different genes. *RPE65* is one of these disease-causing genes. *RPE65* mutation-associated hereditary retinal dystrophy is an orphan disease which affects 1,000-2,000 patients in the US.

Biallelic mutations in the *RPE65* gene have been associated with clinical phenotype of Leber congenital amaurosis Type 2 (LCA2) and with clinical phenotype of retinitis pigmentosa type 20 (RP20). Both LCA2 and RP20 are inherited in an autosomal recessive manner. In patients with retinal dystrophy due to biallelic *RPE65* mutation, the deficiency of the *RPE65* isomerase impairs the ability of retinal pigment epithelium (RPE) cells to respond to light. The accumulation of toxic precursors proximal to the block leads eventually to death of RPE cells. Therefore, patients with biallelic *RPE65* mutation-associated retinal dystrophy suffer from severe and progressive visual deterioration. Almost all patients eventually progress to total blindness.

### 2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

There is no pharmacological treatment available for patients with vision loss due to biallelic *RPE65* mutation-associated retinal dystrophy. The clinical management is supportive, such as use of low-vision aids, and orientation and mobility training.

## 2.4 Previous Human Experience with the Product (Including Foreign Experience)

The first-in-human study for voretigene neparvovec was Study 101, which was part of this BLA submission (see Table 2). Study 102 followed and treated the second eye of those subjects in Study 101.

## 2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Table 1 summarizes the important interactions between the FDA and the applicant during the clinical development of voretigene neparvovec.

**Table 1. Summary of Pre- and Post-Submission Regulatory Activities**

Date	Milestones
9/20/2005	Pre-IND teleconference
6/14/2007	IND 13408 submission by Children’s Hospital of Philadelphia
6/24/2008	Orphan Drug Designation granted for treatment of Leber congenital amaurosis due to <i>RPE65</i> mutation (LCA2)
1/13/2014	IND was transferred to Spark Therapeutics, Inc. (the Applicant of the BLA)
9/24/2014	Breakthrough Therapy Designation granted
3/25/2016	Pre-BLA Meeting
4/26/2016	BLA 125610 rolling submission part 1: Nonclinical section
11/29/2016	Orphan Drug Designation granted for the treatment of inherited retinal dystrophy due to biallelic <i>RPE65</i> mutations
2/21/2017	BLA rolling submission part 2: Clinical section
5/16/2017	BLA rolling submission part 3: CMC section
7/14/2017	BLA Accepted for filing
10/12/2017	Advisory Committee Meeting
1/14/2018	PDUFA action due date

Source: Modified from FDA Briefing Document for Advisory Committee Meeting.

## 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

### 3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

## 5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

All data sources are included in the applicant’s eCTD submission located in the FDA/CBER Electronic Document Room (EDR).

## 5.1 Review Strategy

The applicant submitted three clinical studies in support of this BLA application (Table 2). Of the three trials, Study 301 was the pivotal study designed to evaluate the efficacy and safety of the proposed product. Both Study 101 and Study 102 were Phase I studies, and they were included to provide supportive evidence for safety evaluations. The focus of this review memo is the efficacy and safety evaluation of Study 301.

## 5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The documents reviewed in the original submission STN 125610/0 include:

- Draft Labeling (module 1.14.1.3)
- Clinical Overview (module 2.5)
- Summary of Clinical Efficacy (module 2.7.3)
- Summary of Clinical Safety (module 2.7.4)
- Clinical Study Report (CSR) and tabulations for Study 301 (module 5.3.5.1)
- Statistical Analysis Plan for Study 301 (SAP, Version 4.0) (module 5.3.5.1)
- Study protocol for Study 301 (Version 6) (module 5.3.5.1)
- CSR for Mobility Test Validation Study (module 5.3.5.4)
- Clinical Information Amendment (module 1.11.3)

Analyses performed within this review are based on the following analysis-ready datasets provided by the applicant.

- adsl.xpt, adae.xpt , adlux.xpt, adff.xpt, adhv.xpt, adgv.xpt, adva.xpt (module 5.3.5.1)

## 5.3 Table of Studies/Clinical Trials

Three clinical studies (Study 301, 101 and 102) in this original BLA submission are summarized in Table 2.

**Table 2. Clinical Studies for Voretigene Neparvovec**

Study ID and Period	Study Center(s)	Study Design and Period	Number of Subjects	Treatment Dosage and Route of Administration
Study 301 (Pivotal)	CHOP*  University of Iowa	Phase 3, multicenter, open label, randomized, controlled study  [15-Nov-2012 to 18-May-2016]	Treatment: 21  Control:10	1.5x10 <sup>11</sup> vg to each eye; sequential subretinal injections within 6 to 18 days (12±6 days)
Study 101 (Supportive)	CHOP*	Phase 1, open label, dose escalation study  [25-Sep-2007 to 14-Oct-2014]	Treatment: 12	1.5x10 <sup>10</sup> vg, 4.8x10 <sup>10</sup> vg, or 1.5x10 <sup>11</sup> vg; subretinal; single, unilateral dose
Stud 102 (Supportive)	CHOP*	Phase 1, open label, follow-on study to Study 101  [15-Nov-2010 to 10-Oct-2014]	Treatment: 11	1.5x10 <sup>11</sup> vg; subretinal; single, previously uninjected contralateral eye

\*CHOP = Children’s Hospital of Philadelphia

## 5.4 Consultations

### 5.4.1 Advisory Committee Meeting (if applicable)

A meeting of the Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC) was held on October 12, 2017 to discuss the safety and effectiveness of voretigene neparvovec.

The advisory committee discussed the scoring instrument (see Section 6.1.8 for details) used in the primary efficacy endpoint. Committee members agreed that the instrument attempts to mimic daily ambulatory tasks under different illumination conditions. However, some committee members expressed concern that the primary efficacy endpoint is scored using an ordinal scale, rather than physical illuminance levels in log unit, possibly entailing a loss of information. As the 7 pre-specified lux levels were unevenly spaced, a two-score change in the ordinal scale means different level of improvement in illuminance level depending on the starting score. This could consequently make the interpretation of ordinal scores difficult.

The following voting question was posed to the committee:

“Considering the efficacy and safety information provided in the briefing document, as well as the presentations and discussions during the AC meeting, does voretigene neparvovec have an overall favorable benefit-risk profile for the treatment of patients with vision loss due to confirmed biallelic *RPE65* mutation-associated retinal dystrophy?”

The advisory committee unanimously (16-0) voted that there was an overall favorable benefit-risk profile for voretigene neparvovec for the treatment of patients with vision loss due to confirmed biallelic *RPE65* mutation-associated retinal dystrophy.

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Study 301

Study 301 was a Phase 3 trial and conducted under IND 13408. Results from Study 301 form the primary evidence for evaluating the efficacy and safety of voretigene neparvovec for this BLA application.

#### 6.1.1 Objectives (Primary, Secondary, etc)

The primary objective was to determine whether sequential (non-simultaneous), bilateral subretinal administration of voretigene neparvovec improved the ability to navigate a course with obstacles (as measured by mobility testing) in patients with *RPE65* mutations.

The secondary objective was to assess the safety and tolerability of voretigene neparvovec administrations.

#### 6.1.2 Design Overview

This was a Phase 3, open-label, randomized, controlled trial of gene therapy intervention by sequential subretinal administration of voretigene neparvovec. Following the screening and confirmation of study eligibility, subjects were randomized in a 2:1 allocation ratio into treatment or control groups using a block randomization stratified by

- Age ( $\geq 10$  years vs.  $< 10$  years)
- Mobility testing passing level (pass at  $\geq 125$  lux vs.  $< 125$  lux) as determined at Screening.

Subjects randomized to the treatment group were to receive sequential subretinal injections of voretigene neparvovec in each eye within an 18-day period ( $12 \pm 6$  days). Subjects randomized to the control group were not to receive voretigene neparvovec for a period of at least one year from baseline evaluations. In general, the investigators selected the worse performing eye as the first eye to receive the treatment. The protocol, however, did not specify criteria by which to make the selection of the first eye and each investigator's criteria could be different.

Following repeated retinal and visual function analysis at one month (Day 30), three months (Day 90), six months (Day 180), and one year (Day 365) for both groups, subjects in the control group were crossed over to receive sequential subretinal injections of voretigene neparvovec to each eye (also within 18 days), provided they still met all study eligibility criteria (Figure 1). It should be noted that the post-crossover portion of Study 301 was administratively referred to as Study 302 by the applicant.

All subjects were planned to be followed up to 15 years for safety assessments.

**Figure 1. Study Design.**

Source: FDA clinical review.

6.1.3 Population

Main inclusion criteria were:

- Three years of age or older
- Diagnosis of LCA due to *RPE65* mutation(s) in both alleles
- Visual acuity worse than 20/60 (LogMAR 0.48) in both eyes and/or visual field less than 20° in any meridian, as measured by a III4e isopter or equivalent in both eyes
- Able to perform a MLMT, but unable to pass the MLMT at 1 lux, the lowest luminance level tested

Main exclusion criteria were:

- Subjects with insufficient viable retinal cells as determined by optical coherence tomography (OCT), e.g., areas of retina with thickness measurements less than 100 µm, or absence of neural retina
- Intraocular surgery within prior six months

6.1.4 Study Treatments or Agents Mandated by the Protocol

Voretigene neparvovec is an AAV type 2 vector with the CMV enhancer and the CβA promoter driving expression of human *RPE65* kilodalton protein. A dose of  $1.5 \times 10^{11}$  vg voretigene neparvovec in a total volume of 300 µL was to be injected into the subretinal space of each eye.

#### 6.1.6 Sites and Centers

The subjects were recruited at either The Children's Hospital of Philadelphia (CHOP) or University of Iowa.

#### 6.1.7 Surveillance/Monitoring

An independent Data Safety Monitoring Board (DSMB), which included a statistician, was to meet to discuss safety and to review interim trial data every six months during periods of active enrollment. All AEs were to be reviewed by the Study Medical Monitor and the DSMB.

#### 6.1.8 Endpoints and Criteria for Study Success

##### Primary Efficacy Endpoint

The primary efficacy endpoint was the performance on the MLMT using both eyes, as measured by MLMT score change, one year following vector administration as compared to subjects' baseline MLMT performance.

The Applicant designed the MLMT to assess functional vision, i.e., the ability of a subject to navigate the course accurately and at a reasonable pace at different light levels.

The test layout was standardized for number of obstacles, number of turns, size of arrows, and type of obstacles. There were a total of twelve different configurations in use. The path for the subject to follow was indicated with standardized black arrows on a white background on the floor. The course pattern was changed prior to each run.

MLMT was conducted using the following seven specified light levels: 1, 4, 10, 50, 125, 250 and 400 lux. The corresponding real-world conditions ranged from moonless summer night (1 Lux) to office environment (400 Lux).

The MLMT was performed at Baseline, Days 30, 90, 180 and 365 using the first-treated eye, the second-treated eye, and both eyes sequentially. At each visit, after 40 minutes of dark adaptation, at one light level, subjects completed a randomly selected course of MLMT with one eye patched, then completed a new configuration of the course with the other eye patched, and then completed a new configuration of the course using both eyes. This process was repeated for at least two light levels (one failing and one passing) to identify the failing and passing levels for each eye and for both eyes. The process proceeded from a lower light level to a higher light level.

Every run of the MLMT course was videotaped using high-definition cameras capable of capturing clear images at low illuminance. Trained, masked reviewers (readers) scored each recording. Both speed, defined as the time to complete the course, and accuracy, defined as avoidance of obstacles, were used to determine whether a subject passed or failed each individual run.

The MLMT scores were assigned according to light levels as indicated in Table 3. The differences between the MLMT score at baseline and at the follow-up visits were referred to as the MLMT score changes.

**Table 3. Light Levels and Score Code for MLMT**

<b>Lux</b>	1	4	10	50	125	250	400	>400*
<b>Score code</b>	6	5	4	3	2	1	0	-1

\*Does not pass at 400 lux.

Source: Original BLA 125610/0; Module 5.3.5.1; SAP (v 4.0), p19.

#### Secondary Efficacy Endpoints

- Full-field light sensitivity threshold (FST) testing: change in light sensitivity (averaged over both eyes) for white light at one year as compared to baseline
- MLMT score change from baseline to one year using the first-treated eye
- Visual acuity (VA): change in visual acuity (averaged over both eyes) at one year as compared to baseline

#### Safety Endpoints

Safety endpoints included incidence of AEs, concomitant medications usage, physical examinations, ophthalmic exams, laboratory tests, immunology studies and vector shedding analyses.

#### 6.1.9 Statistical Considerations & Statistical Analysis Plan

##### Sample Size

With a 2:1 ratio, a total of 24 subjects (16 in the treatment group and 8 in the control group) would provide nearly 100% power to detect a median MLMT score change of 1 or more for treatment arm as compared to the control arm (no change) at a two-sided Type I error rate of 0.05. The sample size and power calculation were based on simulations using a Wilcoxon rank sum test with an exact p-value.

##### Analysis Populations

- Intent-to-treat (ITT) population:  
The ITT population included all randomized subjects.
- Modified intent-to-treat (mITT) population:  
The mITT population was comprised of all randomized subjects who did not withdraw, or were not withdrawn.
- Per protocol (PP) population:  
The Per Protocol population was comprised of all mITT subjects excluding subjects who did not receive both injections for the treatment group.
- Safety population:  
The safety population was comprised of all subjects who received at least one injection in either eye for the treatment group and all control group subjects who did not withdraw, or were not withdrawn, prior to any of the following people

knowing the treatment assignment: the subject, parent, Principal Investigator, or Medical Monitor.

The ITT population was specified as the primary analysis population for all analyses of efficacy endpoints. The mITT and PP populations were used for sensitivity and supportive analyses of the primary and secondary efficacy endpoints. The Safety population was used for summaries of safety endpoints.

#### Analysis for Primary Efficacy Endpoint

The primary efficacy endpoint was analyzed using a non-parametric permutation test based on a Wilcoxon rank sum test statistic. The approach was to re-randomize the allocation of treatment label to subject and to calculate the test statistic from the Wilcoxon rank sum test. This process would be repeated 10,000 times. A p-value is then computed based on the empirical distribution of the test statistic as the proportion of test statistics that were smaller than the value observed in the actual dataset.

The primary efficacy endpoint was considered statistically significant if the permutation test p-value was less than 0.05.

#### Analysis for Secondary Efficacy Endpoints

The secondary efficacy endpoints were only to be formally tested only if the primary efficacy endpoint was statistically significant. To control the overall Type I error rate, the three secondary endpoints were to be tested hierarchically in the following order:

- Change in the FST testing
- MLMT score change using the first-treated eye
- Change in VA

Each of the three endpoints was to be tested at a two-sided Type I error rate of 0.05.

The analysis of MLMT score change using the first-treated eye was to use the same statistical approach as described for the primary efficacy endpoint.

For the analysis of FST and VA, a separate model was to assess the magnitude of the difference in response by comparing results at one year with those at baseline. A linear contrast from a repeated measures general linear model assessing change in response was to be used to estimate the magnitude of these effects. The model was to be used with inclusion of the following categorical covariates:

- time as defined by study visit for Baseline, Day 30, Day 90, Day 180, and Day 365 (one year)
- study group
- time by study group interaction

The model was to be used with an unstructured correlation structure to model within-subject correlations. The estimated mean change from baseline to one year and its 95% confidence interval (CI) was to be calculated from the model.

#### Interim Analysis

There was no formal interim analysis planned or conducted for this study.

### Missing Data Handling

Four types of missing data could occur for the primary efficacy endpoint and they were planned to be handled as follows.

- If subjects were removed from the study on the day of randomization, these subjects will be assigned a score change of 0;
- If one of the two MLMT scores using both eyes was missing at baseline or at one year, the individual eye data for that same light level was used to impute the missing score.
- If all data were missing for the baseline assessments, the screening data was to be used. If all data were missing for the one year assessments, the Day 180 data was to be used to impute.
- If the light levels tested at baseline produced only passing scores, the screening results were to be used to establish the necessary cutoff levels.

#### 6.1.10 Study Population and Disposition

##### 6.1.10.1 Populations Enrolled/Analyzed

Table 4 shows a summary of the study analysis sets. Of the 31 subjects randomized, 31 (100%) subjects were included in the ITT population, 29 (94%) were included in the mITT and safety populations, and 28 (90%) were included in the PP population.

**Table 4. Analysis Populations**

<b>Category</b>	<b>Treatment N (%)</b>	<b>Control N (%)</b>	<b>Overall N (%)</b>
Randomized	21 (100%)	10 (100%)	31 (100%)
ITT population	21 (100%)	10 (100%)	31 (100%)
mITT population	20 (95%)	9 (90%)	29 (94%)
PP population	19 (90%)	9 (90%)	28 (90%)
Safety population	20 (95%)	9 (90%)	29 (94%)

Source: Original BLA 125610/0; Module 5.3.5.1; CSR, p84.

##### 6.1.10.1.1 Demographics

Demographics are summarized by study groups for ITT population in Table 5. Overall, subjects ranged from 4 to 44 years old. Twenty subjects were under 18 years of age (20/31, 64%). There were slightly more females (58%) than males (42%) and subjects were primarily white (68%). The subject demographics of the two study groups were approximately balanced, except that all six of the subjects in the 11 – 17 age range were randomized to the treatment group.

**Table 5. Demographics (ITT)**

<b>Category</b>	<b>Treatment (N=21)</b>	<b>Control (N=10)</b>	<b>Total (N=31)</b>
<b>Age (Years)</b>			
Mean (SD)	14.7 (11.8)	15.9 (9.5)	15.1 (10.9)
Quartiles (Q <sub>1</sub> , Median, Q <sub>3</sub> )	6,11,18	9,14,24	6,11,20
Range (min, Max)	4, 44	4, 31	4, 44
<b>Age Groups (Years), n (%)</b>			
4-10	9 (42%)	5 (50%)	14 (45%)
11-17	6 (29%)	0	6 (19%)
>17	6 (29%)	5 (50%)	11 (36%)
<b>Sex, n (%)</b>			
Male	9 (43%)	4 (40%)	13 (42%)
Female	12 (57%)	6 (60%)	18 (58%)
<b>Race, n (%)</b>			
White	14 (66%)	7 (70%)	21 (68%)
Asian	3 (14%)	2 (20%)	5 (16%)
American Indian or Alaska Native	2 (10%)	1 (10%)	3 (10%)
Black or African American	2 (10%)	0	2 (6%)

Source: FDA statistical reviewer's analysis.

#### 6.1.10.1.3 Subject Disposition

Overall, 36 subjects were screened. Five subjects were determined to be ineligible at screening and 31 subjects were randomized. Twenty-one subjects were randomized to the treatment group and 10 subjects were randomized to the control group. One subject randomized in the treatment group did not receive voretigene neparvovec per physician decision due to severe retinal atrophy during the baseline assessments and one subject randomized in the control group withdrew their consent prior to beginning baseline assessments. Table 6 shows the detailed subject disposition.

**Table 6. Subject Disposition**

Category	Treatment N (%)	Control N (%)	Overall N (%)
Randomized	21 (100%)	10 (100%)	31 (100%)
Completed study with one-year assessment	20 (95%)	9 (90%)	29 (94%)
Discontinued before treatment	1 (5%)	1 (10%)	2 (6%)
Withdrawal of consent	0	1 (10%)	1 (3%)
Physician decision	1 (5%)	0	1 (3%)
Crossover to treatment group after one- year	N/A	9 (90%)	9 (90%)
Injected in both eyes	20 (95%)	9 (90%)	29 (94%)

Source: Modified from original BLA 125610/0; Module 5.3.5.1; CSR, p79.

### 6.1.11 Efficacy Analyses

#### 6.1.11.1 Analyses of Primary Endpoint(s)

A summary of the MLMT score change using both eyes at one year compared to baseline for the ITT population is shown in Table 7. The mean (SD) of MLMT score change was 1.8 (1.1) for the treatment group and 0.2 (1.0) for the control group. The median MLMT score change was 2 for the treatment group and 0 for the control group. The MLMT score change at the one-year follow-up visit (i.e. the primary efficacy endpoint) is statistically significantly different between two study groups based on a Wilcoxon Rank-Sum test using an exact method (p-value = 0.001) as well as the permutation test (p-value = 0.001) described in Section 6.1.9. Similar analyses in the mITT population and the PP population showed consistent results in favor of the treatment group (Table 8).

**Table 7. MLMT Score Change Using Both Eyes at One Year Compared to Baseline (ITT)**

MLMT Score Change	Treatment (N=21)	Control (N=10)
Mean (SD)	1.8 (1.1)	0.2 (1.0)
Quartiles (Q1, Median, Q3)	1, 2, 3	-1, 0, 1
Range (min, max)	0, 4	-1, 2

Source: Modified from original BLA 125610/0; Module 5.3.5.1; CSR, p94.

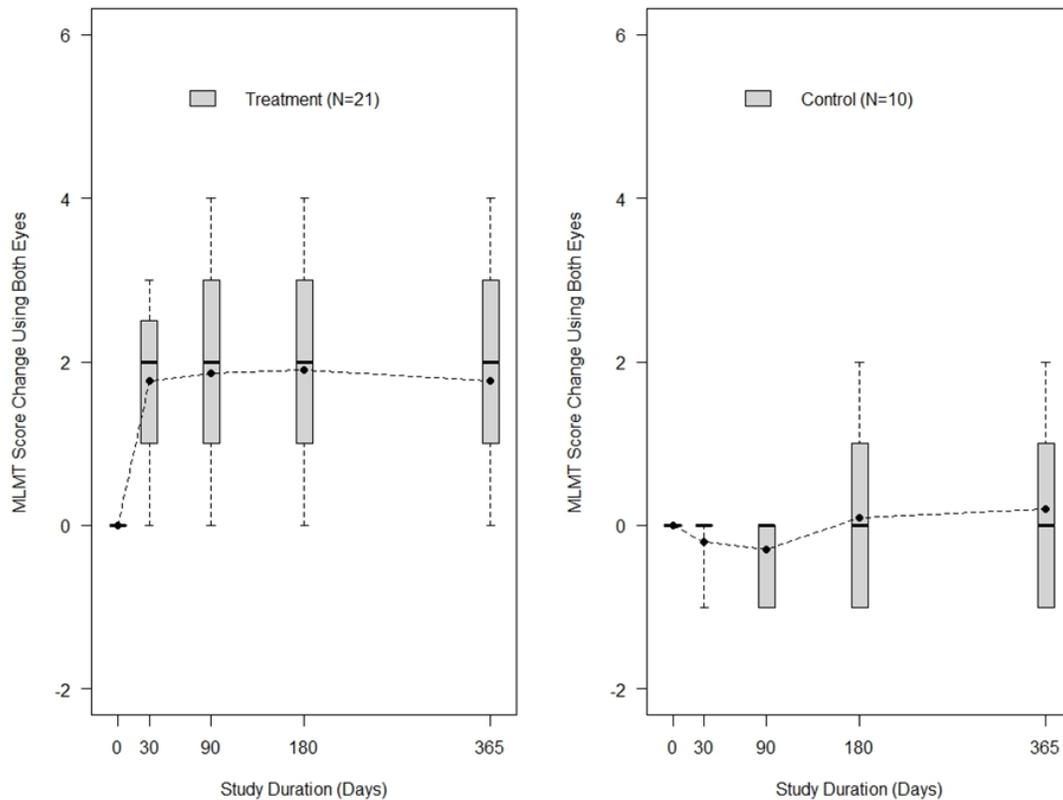
**Table 8. MLMT Score Change Using Both Eyes at One Year Compared to Baseline (mITT and PP)**

MLMT Score Change	mITT		PP	
	Treatment (N=20)	Control (N=9)	Treatment (N=19)	Control (N=9)
Mean (SD)	1.9 (1.0)	0.2 (1.1)	1.9 (1.0)	0.2 (1.1)
Quartiles (Q1, Median, Q3)	1, 2, 3	-1, 0, 1	1, 2, 3	-1, 0, 1
Range (min, max)	0, 4	-1, 2	0, 4	-1, 2

Source: Modified from original BLA 125610/0; Module 5.3.5.1; CSR, p97-98.

The box plots in Figure 2 depict the distribution of MLMT score change using both eyes for the treatment group and the control group at all the follow-up visits during the 1-year study period based on ITT population. A median MLMT score change of 2 was observed in the treatment group at Day 30 and sustained throughout the subsequent follow-up visits. In contrast, a median MLMT score change of 0 was observed in the control group for all the follow-up visits.

**Figure 2. MLMT Score Change Over Time Using Both Eyes (ITT)**



Source: FDA statistical reviewer's analysis.

Table 9 displays the number and percentage of subjects with different magnitudes of MLMT score change using both eyes from baseline to one year by study groups based on ITT population. Eleven subjects (11/21, 52%) in the treatment group had an MLMT score change of 2 or above, while only one subject (1/10, 10%) in the control group had an MLMT score change of at least 2.

**Table 9. Magnitudes of MLMT Score Change Using Both Eyes (ITT) at One Year**

MLMT Score Change	Treatment (N=21)	Control (N=10)
-1	0	3 (30%)
0	2 (10%)	3 (30%)
1	8 (38%)	3 (30%)
2	5 (24%)	1 (10%)
3	5 (24%)	0
4	1 (4%)	0

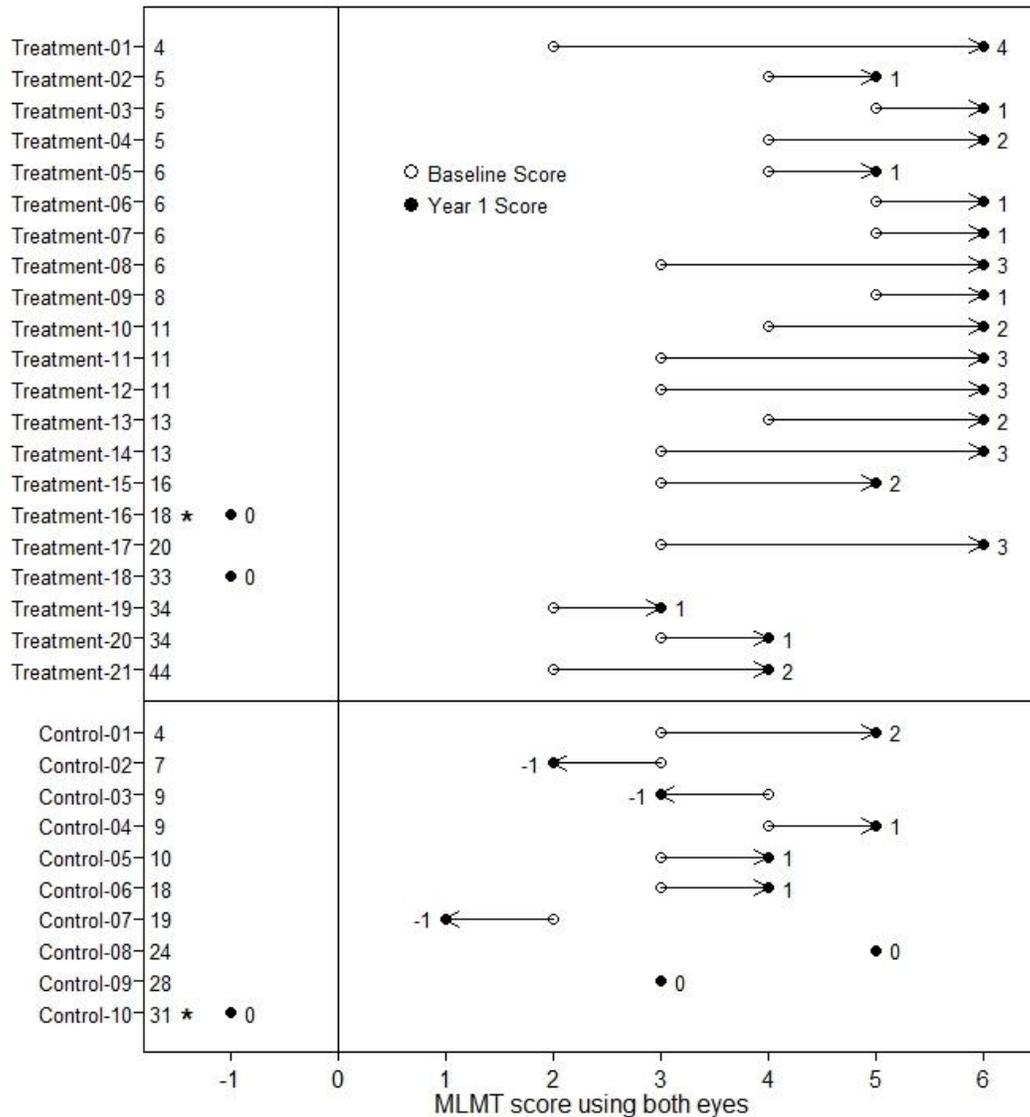
Source: FDA statistical reviewer's analysis.

Figure 3 is a swimmer plot that summarizes the MLMT score using both eyes at baseline and one year for each subject. The top section displays the MLMT scores for the subjects (N=21) in the treatment group. The bottom section displays the MLMT scores for the subjects (N=10) in the control group. Subjects in each study group are chronologically organized by age. There is no evidence of a correlation between MLMT score change and age. The three subjects with an MLMT score of -1 did not pass the MLMT at the 400-Lux light level. Neither of the two subjects in the treatment group with baseline scores of -1 had any improvement in the MLMT, which suggests that subjects with more advanced disease may be less likely to improve with voretigene neparvovec, although the number of such subjects is too small to draw any firm generalizations.

*Reviewer's comment*

*Four out of eight subjects in the treatment group had a baseline score of 5. As the maximum MLMT score is 6, the greatest possible change score these subjects could achieve was 1. All four of these subjects achieved their maximum change score of 1. This ceiling effect could lead to a systematic underestimation of the effect of treatment.*

Figure 3. MLMT Score Using Both Eyes for Individual Subject (ITT)



\*: One subject randomized in the treatment group did not receive the treatment and one subject randomized in the control group withdrew the consent.

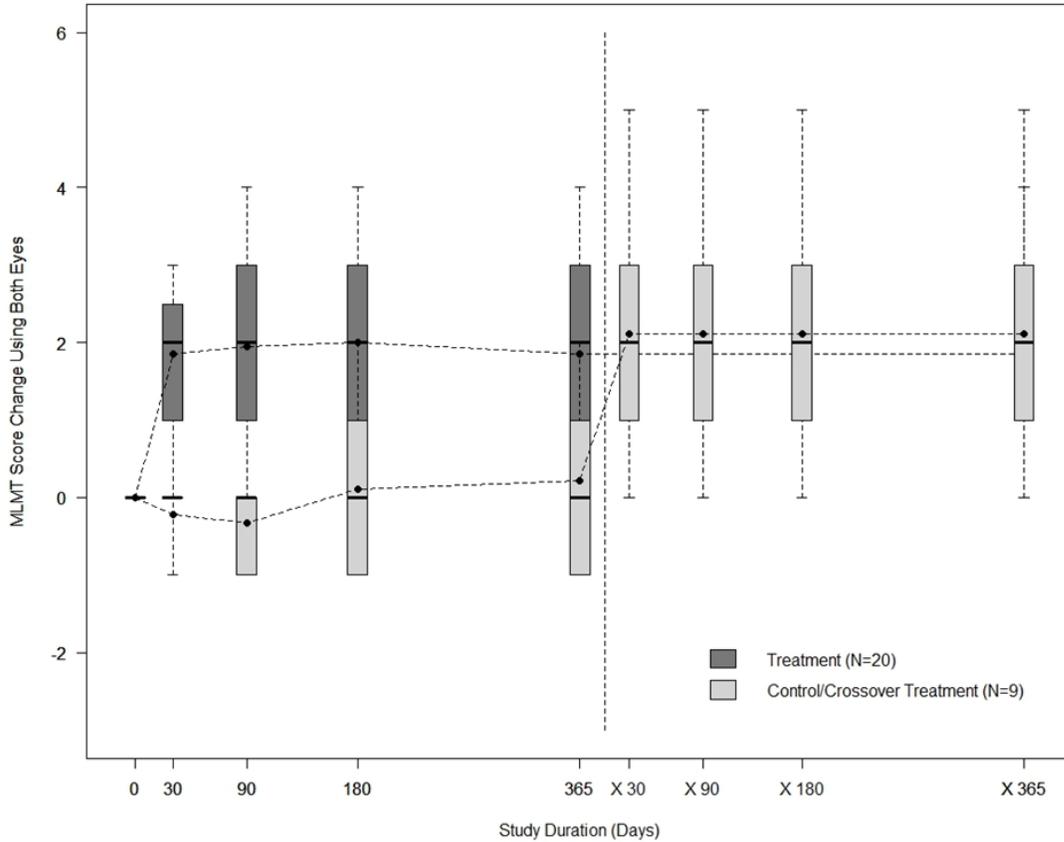
Age at randomization is next to the Subject Number;  
Score change is displayed next to the Year 1 MLMT score.

Source: FDA statistical reviewer's analysis.

After the one-year evaluation, 9 of the 10 subjects in the control group were crossed over to receive subretinal injection of voretigene neparvovec in both eyes. The following box plot (Figure **Error! Reference source not found.**4) shows the MLMT score change using both eyes for the nine subjects in Study 302. A median MLMT score change of 2 for the nine subjects was observed on Day 30 after receiving voretigene neparvovec and maintained throughout the one-year follow-up period. Figure 6 also shows that the

median MLMT score change of 2 in the treatment group (N=20) in Study 301 was maintained throughout the 2-year follow-up period.

**Figure 4. MLMT Score Change Using Both Eyes in Study 301 and 302 (mITT)**



Source: FDA statistical reviewer's analysis.

#### 6.1.11.2 Analyses of Secondary Endpoints

Because there was a statistically significant difference in the primary efficacy endpoint, the three secondary endpoints were tested hierarchically as described in Section 6.1.9.

#### FST testing

The FST results were transformed from decibels (dB), the original relative unit of measurement, to  $\log_{10}(\text{cd.s/m}^2)$ . Smaller  $\log_{10}(\text{cd.s/m}^2)$  values indicate better sensitivity. A summary of FST results based on available data using a longitudinal repeated measures model is shown in Table 10.

**Table 10. FST sensitivity testing: white light [Log10(cd.s/m<sup>2</sup>)]**

	Treatment	Control	Difference (95% CI)	p-value
<b>Both eyes</b>				
N	19	9		
Mean (SE)	-2.08 (0.29)	0.04 (0.44)	-2.11 (-3.19, -1.04)	< 0.001
<b>First-treated eye</b>				
N	19	9		
Mean (SE)	-2.21 (0.30)	0.12 (0.45)	-2.33 (-3.44, -1.22)	< 0.001
<b>Second-treated eye</b>				
N	19	9		
Mean (SE)	-1.93 (0.31)	-0.04 (0.46)	-1.89 (-3.03, -0.75)	0.002

Source: Modified from original BLA 125610/0; Module 5.3.5.1; CSR, p112, 114 and 115.

The analysis of the FST results averaged over both eyes showed a mean (SE) change from baseline to one year of -2.08 (0.29) log<sub>10</sub>(cd.s/m<sup>2</sup>) for the treatment group and 0.04 (0.44) log<sub>10</sub>(cd.s/m<sup>2</sup>) for the control group. The treatment difference between groups of -2.11 (-3.19, -1.04) log<sub>10</sub>(cd.s/m<sup>2</sup>) was statistically significant (p < 0.001). Similar results were observed for the analyses of the FST data using the first-treated eye and second-treated eye (Table 10).

MLMT score change using the first-treated eye

A summary of the MLMT score change using first-treated eye at one year compared to baseline for the ITT population is shown in Table 11. The mean (SD) of MLMT score change was 1.9 (1.2) for the treatment group and 0.2 (0.6) for the control group. The median MLMT score change was 2 for the treatment group and 0 for the control group. The MLMT score change at the one-year follow-up visit is statistically significantly different between two study groups based on a Wilcoxon Rank-Sum test using an exact method (p-value = 0.003) as well as the permutation test (p-value = 0.001) described in Section 6.1.9.

**Table 11. MLMT Score Change Using First-Treated Eye at One Year Compared to Baseline (ITT)**

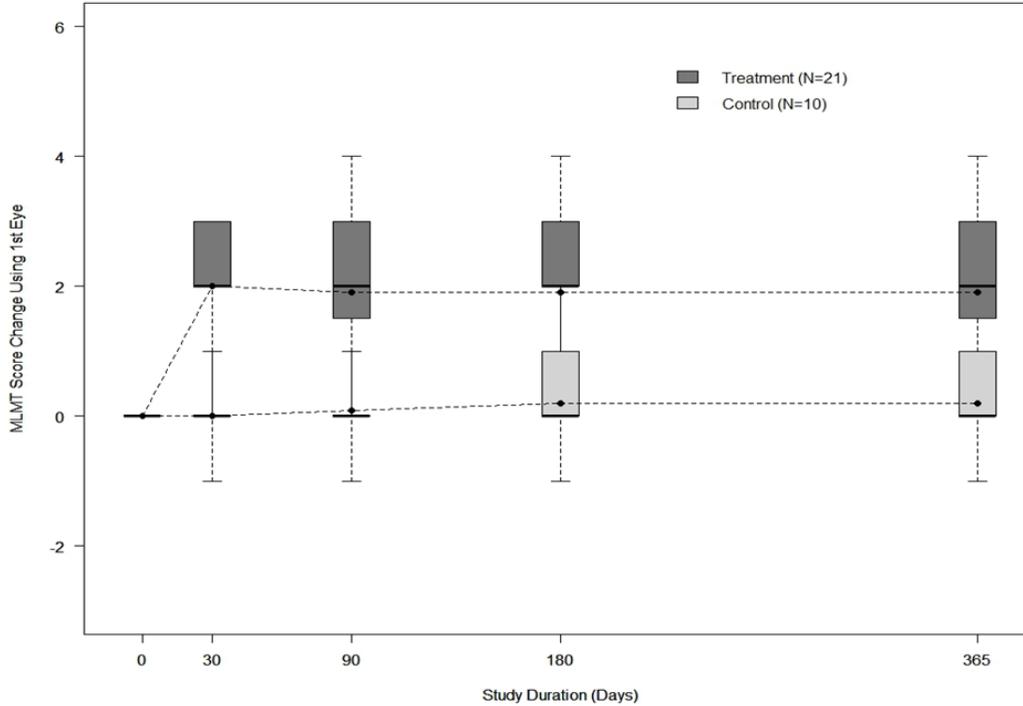
MLMT Score Change	Treatment (N=21)	Control (N=10)
Mean (SD)	1.9 (1.2)	0.2 (0.6)
Quartiles (Q1, Median, Q3)	1, 2, 3	0, 0, 1
Range (min, max)	0, 4	-1, 1

Source: FDA statistical reviewer’s analysis.

The box plots in Figure 5 depict the distribution of MLMT score change using the first-treated eye in the treatment group and the untreated first eye in the control group during the one year follow-up visits. A median MLMT score change of 2 was observed in the treatment group at Day 30 visit following voretigene neparvovec administration and

sustained throughout the one year follow-up period. In contrast, a median MLMT score change of 0 was observed in the control group at all the follow-up visits.

**Figure 5. MLMT Score Change Using the First-Treated Eye**



Source: FDA statistical reviewer's analysis.

Table 12 displays MLMT score change using the first- and second-treated eyes. Using the first-treated eye, 15 subjects (15/21, 71%) in the treatment group had an MLMT score change of 2 or more, whereas no subject in the control group (0/10) showed an MLMT score change of 2 using respective control eyes. Similar results were observed on MLMT score change using the second-treated eye in the treatment group and respective eyes in the control group.

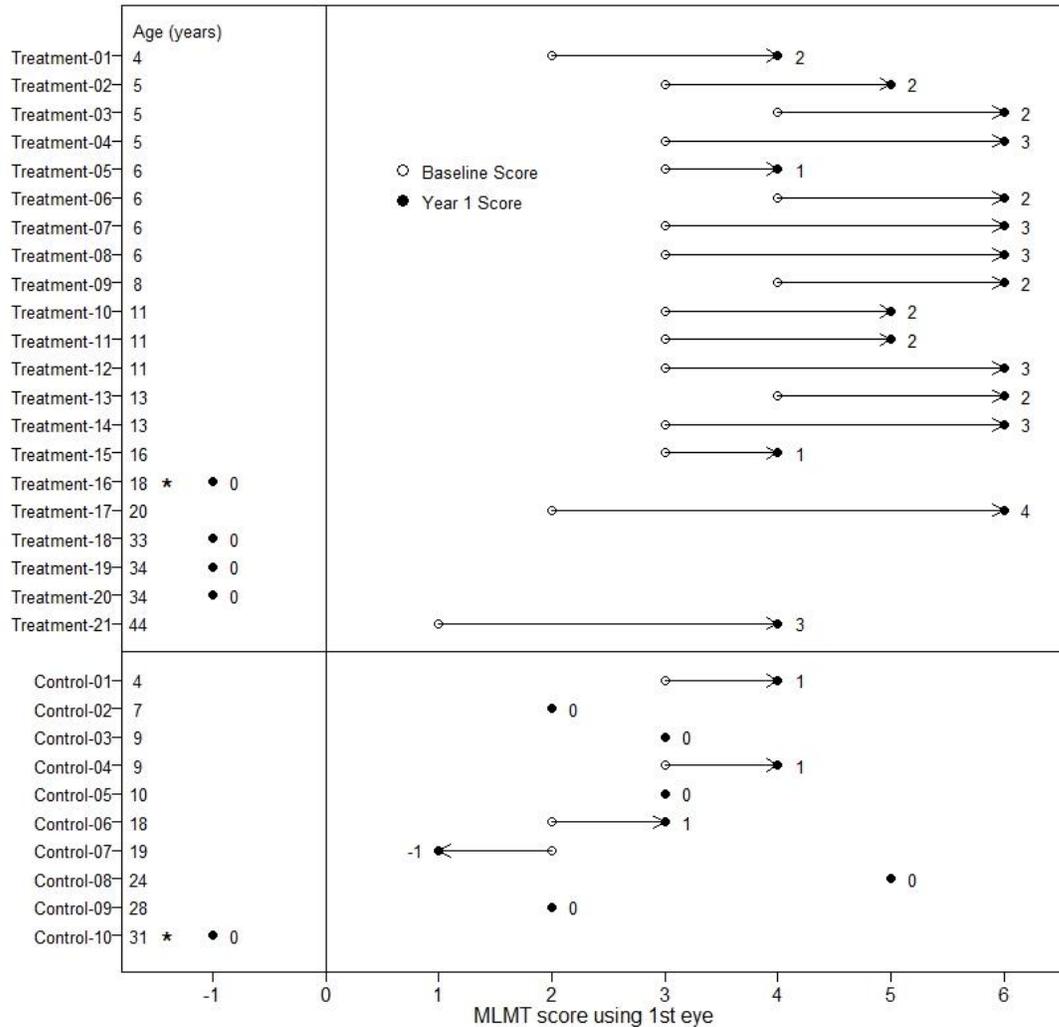
**Table 12. MLMT Score Change Using Single Eye at One Year (ITT)**

<b>Change Score</b>	<b>First-Treated Eye (N=21)</b>	<b>Control (N=10)</b>	<b>Second-Treated Eye (N=21)</b>	<b>Control (N=10)</b>
-1	0	1 (10%)	0	2 (20%)
0	4 (19%)	6 (60%)	2 (10%)	5 (50%)
1	2 (10%)	3 (30%)	4 (19%)	3 (30%)
2	8 (38%)	0	8 (38%)	0
3	6 (28%)	0	5 (23%)	0
4	1 (5%)	0	1 (5%)	0
5	0	0	1 (5%)	0

Source: FDA statistical reviewer's analysis.

Figure 6 is a swimmer plot that summarizes the MLMT score using first-treated eye at baseline and one year for each subject. The top section displays the MLMT scores for the subjects (N=21) in the treatment group. The bottom section displays the MLMT scores for the subjects (N=10) in the control group. Subjects in each study group are chronologically organized by age. Similar to results in Figure 3, there is no clear correlation between MLMT score change for the first-treated eye and age. Four subjects in the treatment group did not show any improvement. At baseline, these subjects could not complete the navigation course at the highest light level of 400 lux, with a score of -1, which suggests that subjects with more advanced disease may be less likely to improve with the treatment.

**Figure 6. MLMT Score Using First-Treated Eye for Individual Subjects (ITT)**



\*: One subject randomized in the treatment group did not receive the treatment and one subject randomized in the control group withdrew the consent.

Age at randomization is next to the Subject Number;  
Score change is displayed next to the Year 1 MLMT score.

Source: FDA statistical reviewer’s analysis.

**Visual Acuity**

VA results are presented in logarithm of the minimum angle of resolution (LogMAR) units, where smaller values indicate better acuity (less visual acuity loss). For the VA analyses, a 0.1 improvement in LogMAR corresponds to a 5-letter improvement (or equivalent of one line) on a standard eye chart. A summary of VA results based on a longitudinal repeated measures model using available data is shown in Table 13. Analysis of VA averaged over both eyes showed a mean (SE) change from baseline to one year of -0.16 (0.07) LogMAR for the treatment group and 0.01 (0.10) LogMAR for the control group, resulting in a mean (95% CI) treatment-effect difference of -0.16 (-0.41, 0.08); this difference was not statistically significant (p = 0.17). Similar results were observed for the analyses of VA data using first- and second-treated eyes.

**Table 13. VA [LogMAR]**

	Treatment	Control	Difference (95% CI)	p-value
<b>Both eyes</b>				
N	20	9		
Mean (SE)	-0.16 (0.07)	0.01 (0.10)	-0.16 (-0.41, 0.08)	0.17
<b>First-treated eye</b>				
N	20	9		
Mean (SE)	-0.17 (0.11)	-0.03 (0.16)	-0.14 (-0.53, 0.25)	0.46
<b>Second-treated eye</b>				
N	20	9		
Mean (SE)	-0.15 (0.04)	-0.02 (0.06)	-0.13 (-0.28, 0.01)	0.07

Source: Modified from original BLA 125610/0; Module 5.3.5.1; CSR, p112, 114 and 115.

As a supportive analysis, Table 14 compares the VA change between the treatment and control groups at one year after voretigene neparvovec administration. An improvement of LogMAR 0.3 (i.e.  $\leq -\text{LogMAR } 0.3$ ) is considered clinically meaningful per the FDA clinical review team.

At one year, VA improvement of LogMAR 0.3 occurred in 11 (55%) of the first-treated eyes and 4 (20%) of the second-treated eyes; whereas no control group subject had VA improvement of LogMAR 0.3 in either the first- or second-treated eye. Among the 11 subjects who had a 2-level or more score change in MLMT using both treated eyes, a VA improvement of LogMAR 0.3 occurred in seven subjects in the first-treated eye and three subjects in the second-treated eye. Among the nine subjects who did not have a 2-level or more score change in MLMT using both-treated eyes, a VA improvement of LogMAR 0.3 occurred in four subjects in the first-treated eye and no subjects in the second-treated eye.

**Table 14. VA Improvement of LogMAR 0.3 at One Year (mITT)**

Study 301	VA Improvement of LogMAR 0.3 In the First-Treated Eye N (%)	VA Improvement of LogMAR 0.3 In the Second-Treated Eye N (%)
Treatment Group (n=20)	11 (11/20, 55%)	4 (4/20, 20%)
MLMT score change $\geq 2$ (n=11)	7 (7/11, 64%)	4 (4/11, 36%)
MLMT score change $< 2$ (n=9)	4 (4/9, 44%)	0 (0%)
Control Group (n=9)	0 (0%)	0 (0%)

Source: FDA statistical reviewer's analysis.

#### 6.1.11.3 Subpopulation Analyses

Tables 15-18 show the subgroup analysis by age categories, sex, race and study sites using ITT population, respectively. The results show a similar trend as the primary efficacy analysis in favor of treatment group in each subgroup.

**Table 15. MLMT Score Change Using Both Eyes at One Year Compared to Baseline by Age Groups (ITT)**

<b>Age Groups (Years)</b>	<b>Treatment (N=21)</b>	<b>Control (N=10)</b>
<b>4-10</b>		
N	9	5
Mean (SD)	1.7 (1.1)	0.4 (1.3)
Quartiles (Q1, Median, Q3)	1, 1, 2	-1, 1, 1
Range (min, max)	1, 4	-1, 2
<b>11-17</b>		
N	6	0
Mean (SD)	2.5 (0.5)	--
Quartiles (Q1, Median, Q3)	2, 3, 3	--
Range (min, max)	2, 3	--
<b>&gt;17</b>		
N	6	5
Mean (SD)	1.2 (1.2)	0.0 (0.7)
Quartiles (Q1, Median, Q3)	0, 1, 2	0, 0, 0
Range (min, max)	0, 3	-1, 1

Source: FDA statistical reviewer's analysis.

**Table 16. MLMT Score Change Using Both Eyes at One Year Compared to Baseline by Sex (ITT)**

<b>Sex</b>	<b>Treatment (N=21)</b>	<b>Control (N=10)</b>
<b>Female</b>		
N	12	6
Mean (SD)	2.1 (1.2)	0.2 (1.0)
Quartiles (Q1, Median, Q3)	1, 2, 3	-1, 1, 1
Range (min, max)	0, 4	-1, 1
<b>Male</b>		
N	9	4
Mean (SD)	1.3 (0.9)	0.3 (1.3)
Quartiles (Q1, Median, Q3)	1, 1, 2	-1, 0, 1
Range (min, max)	0, 3	-1, 2

Source: FDA statistical reviewer's analysis.

**Table 17. MLMT Score Change Using Both Eyes at One Year Compared to Baseline by Race (ITT)**

<b>Race</b>	<b>Treatment (N=21)</b>	<b>Control (N=10)</b>
<b>White</b>		
N	14	7
Mean (SD)	1.9 (1.1)	0.1 (0.9)
Quartiles (Q1, Median, Q3)	1, 2, 3	-1, 0, 1
Range (min, max)	0, 4	-1, 1
<b>Asian</b>		
N	3	2
Mean (SD)	1.3 (1.5)	0.5 (2.1)
Quartiles (Q1, Median, Q3)	0, 1, 3	-1, 1, 2
Range (min, max)	0, 3	-1, 2
<b>American Indian or Alaska Native</b>		
N	2	1
Mean (SD)	1.5 (0.7)	0.0 ( NA )
Quartiles (Q1, Median, Q3)	1, 2, 2	0, 0, 0
Range (min, max)	1, 2	0, 0
<b>Black or African American</b>		
N	2	0
Mean (SD)	1.5 (0.7)	--
Quartiles (Q1, Median, Q3)	1, 2, 2	--
Range (min, max)	1, 2	--

Source: FDA statistical reviewer's analysis.

**Table 18. MLMT Score Change Using Both Eyes at One Year Compared to Baseline by Study Sites (ITT)**

<b>Study Sites</b>	<b>Treatment (N=21)</b>	<b>Control (N=10)</b>
<b>Children's Hospital of Philadelphia</b>		
N	11	8
Mean (SD)	1.6 (1.2)	0.3 (1.2)
Quartiles (Q1, Median, Q3)	1, 1, 3	-1, 0.5, 1
Range (min, max)	0, 3	-1, 2
<b>University of Iowa Hospitals and Clinics</b>		
N	10	2
Mean (SD)	1.9 (1.0)	0 (NA)
Quartiles (Q1, Median, Q3)	1, 2, 2	0, 0, 0
Range (min, max)	1, 4	0, 0

Source: FDA statistical reviewer's analysis.

#### 6.1.11.4 Dropouts and/or Discontinuations

Subject dropouts and/or discontinuations are summarized in Table 6. One subject randomized in the treatment group did not receive the treatment and one subject randomized in the control group withdrew the consent. No subjects discontinued the study due to treatment-emergent adverse events (TEAEs).

#### 6.1.12 Safety Analyses

##### 6.1.12.3 Deaths

There were no deaths in this study.

##### 6.1.12.4 Nonfatal Serious Adverse Events (SAEs)

Table 19 summarizes SAEs by study groups. Two (10%) subjects in the treatment group experienced three SAEs at time points distant from vector administration. All the SAEs were considered unlikely to be related to study product or study product administration procedure.

**Table 19. Summary of Treatment-Emergent Serious Adverse Events (Safety)**

<b>Preferred Term, n (%)</b>	<b>Treatment (N = 20)</b>	<b>Control (N = 9)</b>	<b>Overall (N = 29)</b>
Subjects with at least one SAE	2 (10%)	0	2 (7%)
Adverse drug reaction*	2 (10%)	0	2 (7%)
Convulsion	1 (5%)	0	1 (3%)

\* Adverse drug reaction to non-investigational medications.

Source: Modified from original BLA 125610/0; Module 5.3.5.1; CSR, p181.

##### 6.1.12.5 Adverse Events of Special Interest (AESI)

Ocular adverse events were primarily related to the administration procedure. Table 20 lists the incidence of each ocular AE in Study 301. The treatment may cause transient or permanent complications such as increased intraocular pressure, cataract, and retinal defect.

**Table 20. Ocular Adverse Events**

Ocular AEs, n (%)	Subjects (N=20)	Treated Eyes (N=40)
Any ocular AE	12 (60%)	21 (53%)
Intraocular pressure (IOP) increased	4 (20%)	5 (13%)
Cataract development*	4 (20%)	7 (18%)
Retinal tear	2 (10%)	2 (5%)
Eye pain	1 (5%)	1 (3%)
Eye Inflammation	2 (10%)	4 (10%)
Eye irritation	1 (5%)	1 (3%)
Macular hole	1 (5%)	1 (3%)
Maculopathy (including macular pucker)	1 (5%)	2 (5%)
Retinal hemorrhage	1 (5%)	1 (3%)

\*Cataract development includes both extracted and unextracted cataracts.

Source: FDA clinical reviewer and statistical reviewer's analysis.

## 10. CONCLUSIONS

### 10.1 Statistical Issues and Collective Evidence

Study 301 was a Phase 3, open-label, randomized, and controlled trial conducted under IND 13408 in two US study sites. A total of 31 subjects (21 subjects in the treatment group and 10 subjects in the control group) were randomized in the study, ranging in age from 4 to 44 years old. The primary efficacy endpoint was change in performance on the multi-luminance mobility testing (MLMT) using both eyes from baseline to one year following vector administration. The median one-year MLMT score change in the intent-to-treat (ITT) analysis set was 2 for the treatment group and 0 for the control group, a statistically significant difference based on a Wilcoxon Rank-Sum test using an exact method (p-value = 0.001) as well as a permutation test (p-value = 0.001). Further analysis showed that 11 subjects (11/21, 52%) in the treatment group had an MLMT score change of 2 or more, while only one subject (1/10, 10%) in the control group had an MLMT score change of at least 2. Similar analyses for the MLMT score change using both eyes based on modified intent-to-treat (mITT) and per protocol (PP) analysis sets revealed consistent results in favor of the treatment group.

Results for the secondary efficacy endpoints in Study 301 were consistent with those for the primary efficacy endpoint. The analysis of the full-field light sensitivity threshold (FST) using both eyes showed a mean (SE) change from baseline to one year of -2.08 (0.29) log<sub>10</sub>(cd.s/m<sup>2</sup>) for the treatment group and 0.04 (0.44) log<sub>10</sub>(cd.s/m<sup>2</sup>) for the control group based on a longitudinal repeated measures model. The treatment difference (95% CI) between two groups of -2.11 (-3.19, -1.04) log<sub>10</sub>(cd.s/m<sup>2</sup>) was statistically significant (p < 0.001).

The median MLMT score change at one year compared to baseline using first-treated eye was 2 for the treatment group and 0 for the control group. The MLMT score change was

statistically significantly different between two study groups based on a Wilcoxon Rank-Sum test using an exact method (p-value = 0.003) as well as a permutation test (p-value = 0.001). Fifteen (15) subjects (15/21, 71%) in the treatment group had an MLMT score change of 2 or more, whereas no subject in the control group (0/10) showed an MLMT score change of at least 2 using respective control eyes.

A longitudinal repeated measures analysis of visual acuity (VA) averaged over both eyes showed a mean (SE) change from baseline to one year of -0.16 (0.07) LogMAR for the treatment group and 0.01 (0.10) LogMAR for the control group, resulting in a mean (95% CI) treatment-effect difference of -0.16 (-0.41, 0.08). Though the difference is not statistically significant (p = 0.17), it is numerically in favor of voretigene neparvovec treatment.

Among 20 subjects (40 treated eyes) treated with voretigene neparvovec in Study 301, 12 subjects (21 treated eyes) had ocular adverse events (AEs); these were primarily related to the administration procedure. Most ocular AEs were resolved with minimal or no intervention and without sequelae. Two (10%) subjects in the treatment group experienced three serious adverse events (SAEs) at time points distant from vector administration. All SAEs were considered unlikely to be related to study product or study product administration procedure. No deaths occurred. Further analysis of safety data in the submitted three clinical studies is deferred to the clinical review team.

## 10.2 Conclusions and Recommendations

The efficacy results of Study 301 provided statistical evidence to support the proposed indication that administration of voretigene neparvovec improves the ability to navigate a course with obstacles (as measured by MLMT) in patients with vision loss due to confirmed biallelic *RPE65* mutation-associated retinal dystrophy.