DISCLAIMER STATEMENT
The attached package contains background information prepared by the Food and Drug Administration (FDA) for the members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring the Biologics License Application (BLA) for voretigene neparvovec, a first-in-class product, with the Applicant's proposed indication, to this Advisory Committee to gain the Committee’s insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the FDA for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.
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ABBREVIATIONS

AAV         Adeno-associated virus
AAV2-hRPE65v2 AAV serotype 2 carrying the human RPE65 gene, voretigene neparvovec
AE          Adverse event
BCVA        Best-corrected visual acuity
BLA         Biologics License Application
CβA         Chicken beta actin
CCMT        Center for Cellular and Molecular Therapeutics
CHOP        Children’s Hospital of Philadelphia
CMV         Cytomegalovirus
CSR         Clinical Study Report
ELISA       Enzyme-Linked Immunosorbent Assay
FDA         Food and Drug Administration
FST         Full-field light sensitivity threshold
hRPE        Human retinal pigment epithelium
hRPE65      Human retinal pigment epithelium 65 kDa protein
IND         Investigational new drug application
IOP         Intraocular pressure
ITR         Inverted terminal repeat
ITT         Intent to treat
kDa         Kilodalton
LCA         Leber congenital amaurosis
LCA2        Leber congenital amaurosis type 2 (due to RPE65 mutations)
LogMAR      Logarithm of the minimal angle of resolution
MLMT        Multi-luminance mobility testing
OCT         Optical coherence tomography
PBMC        Peripheral blood mononuclear cells
polyA       Polyadenylation
PLR         Pupillary light reflex
RP          Retinitis pigmentosa
RPE         Retinal pigment epithelium
RPE65       Retinal pigment epithelium 65 kDa protein
SAE         Serious adverse event
TEAE        Treatment emergent adverse event
μL          Microliter
VA          Visual acuity
VF          Visual field
Vg          Vector genome
1 CLINICAL INDICATION

The Applicant’s proposed indication for voretigene neparvovec (AAV2-hRPE65v2) is the treatment of patients with vision loss due to confirmed biallelic \textit{RPE65} mutation-associated retinal dystrophy.

2 EXECUTIVE OVERVIEW

Topic

The Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) is being convened to discuss the BLA submitted by Spark Therapeutics, Inc. (the Applicant) for voretigene neparvovec for the treatment of patients with vision loss due to confirmed biallelic \textit{RPE65} mutation-associated retinal dystrophy. Voretigene neparvovec is a recombinant adeno-associated viral vector serotype 2, expressing the gene for human retinal pigment epithelial 65 kilodalton protein (AAV2-hRPE65v2).

Issues

The primary evidence of effectiveness is generated from a randomized, open-label Phase 3 study (Study 301). The study subjects in Study 301 ranged in age from 4 to 44 years. Because of safety concerns, mainly related to the subretinal injection procedure, only subjects who had significant vision loss, defined as visual acuity (VA) worse than 20/60 (LogMAR \footnote{logarithm of the minimal angle of resolution on the LogMAR chart} 0.48) in both eyes and/or visual field (VF) less than 20 degree (20°) in both eyes, were enrolled. Each eye received a one-time subretinal injection of voretigene neparvovec.

The primary efficacy endpoint was improvement in the multi-luminance mobility testing (MLMT). The MLMT was designed to assess functional vision, specifically the ability of a subject to navigate the course accurately and at a reasonable pace at different light levels. This novel outcome measure has not been used as an efficacy endpoint in any other clinical studies.

At one year, a 2-light level or more improvement in MLMT \footnote{i.e., an MLMT score change of 2 or more} occurred in eleven (11) of the 21 (11/21, 52\%) subjects using both-treated eyes and fifteen (15) of the 21 (15/21, 71\%) subjects using the first-treated eye. A median MLMT score change of 2 occurred in the treatment group at Day 30 (using both eyes or the first-treated eye) following voretigene neparvovec administration, and sustained throughout the subsequent follow-up visits through one year. The difference in the median MLMT score change at 1 year, comparing the treatment and control groups, was statistically significant. The data on the duration of the effect
are limited. No clinical data are available on repeat administration of voretigene neparvovec to treat an individual eye.

Visual acuity (VA) was a secondary endpoint. 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 subject had VA improvement of LogMAR 0.3 in either the first or second eye of the control group. However, the mean VA changes were not significantly different, comparing the treatment and control groups, for either the first- or the second-treated eyes, over the duration of the study.

The safety analysis population consists of 41 subjects (81 treated eyes) enrolled in Phase 1 and Phase 3 studies. The adverse events (AEs) include events presumably related to the surgical procedure used to administer the product, events related to the product itself, and events related to the ancillary medications, including prednisone. The more serious AEs include endophthalmitis, macular holes, foveal dehiscence, retinal hemorrhage, retinal tears, elevated intraocular pressure, and cataract development. Some of these events may have long-term consequences.

The FDA seeks the opinion of the Committee regarding the following issues:

1. The clinical meaningfulness of a 2-light level improvement in the multi-luminance mobility testing (MLMT) in “patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy”

2. The optimal disease stage to treat patients with biallelic RPE65 mutation-associated retinal dystrophy, especially:
   a. At what stage of clinical presentation do the benefits of therapy outweigh the risks?
   b. How can the data from subjects with significant vision loss be extrapolated to patients with earlier stages of disease with or without measurable vision loss prior to treatment?
   c. Considering the adverse events associated with the subretinal injection of voretigene neparvovec and the concomitant use of oral prednisone, what are your concerns for treating pediatric patients at a young age?
   d. What is the reasonable minimal age, if any, that you would recommend for treatment?

3. The potential benefits and risks of repeat administration of voretigene neparvovec into one eye, and what, if any, additional data is required to support such repeat administration
3 BACKGROUND

3.1 Regulatory Background

Table 1 is a brief summary of the main interactions between the FDA and the Applicant.

Table 1. Regulatory Milestones

<table>
<thead>
<tr>
<th>Date</th>
<th>Milestones</th>
</tr>
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<tbody>
<tr>
<td>6/14/2007</td>
<td>IND submission by Children’s Hospital of Philadelphia</td>
</tr>
<tr>
<td>6/24/2008</td>
<td>Orphan Drug Designation of AAV2-hRPR65v2 for treatment of Leber congenital amaurosis due to RPE65 mutation (LCA2) (#08-2593)</td>
</tr>
<tr>
<td>1/12/2014</td>
<td>IND transferred to Spark Therapeutics, Inc. (the Applicant)</td>
</tr>
<tr>
<td>9/24/2014</td>
<td>Breakthrough Therapy Designation of AAV2-hRPR65v2 for treatment of Leber congenital amaurosis due to RPE65 mutation</td>
</tr>
<tr>
<td>4/26/2016</td>
<td>BLA rolling submission part 1: Nonclinical section</td>
</tr>
<tr>
<td>11/29/2016</td>
<td>Orphan Drug Designation of AAV2-hRPE65v2 for the treatment of inherited retinal dystrophy due to biallelic RPE65 mutations</td>
</tr>
<tr>
<td>2/21/2017</td>
<td>BLA rolling submission part 2: Clinical section</td>
</tr>
<tr>
<td>5/16/2017</td>
<td>BLA rolling submission part 3: CMC section</td>
</tr>
<tr>
<td>7/14/2017</td>
<td>BLA Accepted for filing</td>
</tr>
</tbody>
</table>

At a meeting on June 16, 2015, FDA agreed that an MLMT score change using both eyes could serve as one of the primary efficacy endpoints for Study 301.

3.2 Product Description

Voretigene neparvovec (AAV2-hRPE65v2) is a recombinant adeno-associated virus serotype 2 (AAV2) vector with a cytomegalovirus (CMV) enhancer and chicken beta actin (CβA) promoter driving expression of the gene for human retinal pigment epithelium 65 kDa protein (hRPE65), an isomerase enzyme.

3.2.1 Adeno-associated virus as a gene therapy vector

Adeno-associated viruses (AAV) are members of the Parvoviridae family. AAV are replication deficient, and are not able to replicate unless cells are co-infected with a helper virus, such as adenovirus. AAV are highly prevalent in the human population with about 70-80% of the population being seropositive for antibodies to various AAV serotypes (i.e., serotypes 1, 2, 3, 5) (Gao et al., 2004). While AAV2 is the most extensively studied serotype and is considered the prototype for the AAV family, more than 100 isolates of AAV have been described (Wu & Samulski, 2006).

The general organization of the AAV genome is conserved across the different serotypes, and is described below in the context of AAV2. AAV2 consists of a single-stranded DNA genome of
about 4.7 kB, which is encapsulated in a protein coat (Srivastava, 1983). The AAV2 genome consists of three elements: the rep gene, the cap gene, and the inverted terminal repeats (ITRs). The rep gene codes for proteins involved in DNA replication, packaging, and integration. The cap gene, encodes three amino terminal virus proteins, VP1, VP2 and VP3 through a differential splicing mechanism (Sonntag 2011). These proteins make up the coat of the virus and are assembled into a well-defined icosahedral structure (Xie, et al, 2002), which results in AAV2 being highly stable and resistant to environmental factors (Rabinowitz et al., 2002).

AAV2 transduces a wide range of tissue types, including liver, muscle, lung and CNS, with moderate efficiency. AAV2 was the first AAV to be developed into recombinant vectors for gene therapy applications, due to AAV2’s lack of pathogenicity, wide range of infectivity, and ability to establish long-term transgene expression (Wu & Samulski, 2006). While a number of other serotypes are currently under investigation for gene therapy applications, nearly all incorporate the AAV2 ITRs.

3.2.2 Voretigene neparvovec

For the recombinant vector voretigene neparvovec, the AAV2 rep and cap genes were replaced with an expression cassette encoding hRPE65. The voretigene neparvovec genome contains the following components: 1) the cytomegalovirus (CMV) enhancer; 2) the chicken beta actin (CβA) promoter; 3) the CβA exon 1 and intron; 4) the cloned cDNA coding for human retinal pigment epithelium 65kDa protein (hRPE65); and 5) the bovine growth hormone polyadenylation (PolyA) region, flanked by AAV2 ITRs. Small intervening non-functional DNA sequences derived in the process of assembling the genetic elements through recombinant DNA techniques are also present. A diagram of the vector genome is provided in Figure 1.

Figure 1. Schematic representation of voretigene neparvovec

Source: Spark BLA

The voretigene neparvovec manufacturing process starts with HEK293 cell culture and expansion, followed by transient transfection with three plasmid constructs. Separate plasmids encode the human RPE65 expression cassette, the AAV2 rep and cap sequences, and the helper virus-derived sequences required for replication of the hRPE65 expression cassette prior to packaging. The transfected cells are harvested, and voretigene neparvovec is purified through multiple processing steps, including final sterile filtration. The Drug Product is formulated as a
frozen aqueous solution that requires a 1:10 dilution with Diluent prior to administration. The formulation includes inactive ingredients sodium chloride, sodium phosphate, and poloxamer 188, which are identical in both the Drug Product and the Diluent.

3.3 Physiologic Role of the Human RPE65 Protein – an Isomerase

The pathway of 11-cis-retinal activity is outlined in Figure 2. Briefly, absorption of a photon ($h\nu$) by a rhodopsin pigment molecule induces isomerization of 11-cis-retinal (11-cis-RAL) to all-trans-RAL. The all-trans-RAL is reduced to all-trans-ROL, transported to the retinal pigment epithelium (RPE), and converted to fatty acid all-trans-retinyl esters by lecithin/retinol acyltransferase (LRAT). The isomerase, RPE-specific 65 kDa protein (RPE65) uses an all-trans-retinyl ester as substrate to form 11-cis-retinol (11-cis-ROL) plus a free fatty acid. Regeneration of 11-cis-retinal via a two-step process that is catalyzed in part by RPE65 completes this retinoid (visual) cycle and is critical for maintaining vision. (Travis 2007).

Figure 2. Visual cycle in retinal pigment epithelium (RPE) cells

3.4 Biallelic RPE65 Mutation-Associated Retinal Dystrophy

Hereditary retinal dystrophies are a broad group of genetic retinal disorders that are associated with progressive visual dysfunction and are caused by mutations in any one of over 220 different genes (RetNet https://sph.uth.edu/retnet/sum-dis.htm; Summaries of Genes and Loci Causing Retinal Diseases). A mutation in the RPE65gene can cause one of these disorders.
Hereditary retinal dystrophies used to be grouped together based on clinical manifestations and findings (phenotype). As mutations in a gene are more directly linked to the underlying molecular pathogenesis, it is now considered more appropriate to categorize this group of disorders by the individual disease-causing gene (genotype). For example, Leber congenital amaurosis (LCA), a severe clinical subgroup of a retinal dystrophy, was considered as a single phenotypic entity characterized by early onset (usually the first year of life) of profound blindness, nystagmus, sluggish or near-absent pupillary responses, photophobia, high hyperopia, and keratoconus. LCA is now known to be caused by mutations in any one of 19 genes (den Hollander 2016; Astuti 2016). Another example is retinitis pigmentosa (RP), the most common clinical subgroup of retinal dystrophy. RP used to be considered as a single phenotypic entity unified by the presence of night-blindness, progressive visual field loss, eventual acuity loss and bone-spicule retinal pigmentation. It is now known that RP is genetically heterogeneous, and mutations in any one of over one hundred genes can cause the phenotype.

In patients with retinal dystrophy due to biallelic RPE65 mutations, the deficiency of RPE65 isomerase leads to the inability to regenerate 11-cis-retinal, via 11-cis-retinol, in the RPE cells. This impairs the ability of RPE cells to respond to light. In addition, the accumulation of toxic precursors proximal to the block leads eventually to death of RPE cells, which results in death of photoreceptors (Redmond 1998; Katz 2001) and the subsequent clinical sequelae. Biallelic mutations in the RPE65 gene have been associated with the clinical phenotype of Leber congenital amaurosis Type 2 (LCA2) and with the clinical phenotype of retinitis pigmentosa type 20 (RP20). Both LCA2 and RP20 are inherited in an autosomal recessive manner. The prevalence of LCA2 is approximately 0.74 – 1.5 per one million and accounts for approximately 1% or less of all retinal dystrophies (Stone, 2007; den Hollander et al., 2008). The estimated prevalence of RP20 is approximately 5 per one million (Fahim 1993-2014; Morimura 1998; Thompson 2000; Wang 2014).

There is no approved pharmacological treatment available for biallelic RPE65 mutation-associated retinal dystrophy. The clinical management is supportive, such as use of low-vision aids, and orientation and mobility training. However, the Argus II Retinal Prosthesis System, an implanted device, was approved in the United States in 2013 under Humanitarian Device Exemption (HDE) for the treatment of adult patients with severe vision loss (bare light or no light perception in both eyes) from advanced retinitis pigmentosa.

3.5 Mechanism of Action of voretigene neparvovec

The product voretigene neparvovec is designed to deliver a normal copy of the gene encoding the human retinal pigment epithelial 65 kDa protein (hRPE65) to cells of the retina in persons lacking a normal functional version of RPE65. The AAV2 capsid components of voretigene neparvovec facilitate cell surface binding, entry, and delivery of the vector genome packaged within the capsid to the nucleus of the cell. Once in the nucleus, the genome is uncoated and replicated by cellular DNA polymerases into a double stranded genome, which subsequently forms extrachromosomal concatemers (multiple copies of the same DNA sequence arranged end to end in tandem, may be circular or linear) of the expression cassette (Duan et al, 1998).
Following delivery and formation of concatemers, voretigene neparvovec achieves efficient and durable expression of the hRPE65 enzyme in cells of the retina.

### 3.6 Concern of AAV Immunogenicity

One safety concern for vector-mediated gene delivery is the potential to generate an immune response (humoral and/or cellular) against the vector, the expressed protein, or both. Such responses could result in inflammation, significant reduction or abrogation of \textit{in vivo} gene expression, or destruction of transduced cells. These reactions could occur in patients who have pre-existing immunity to the vector, de novo, or as a result of re-administration of the gene therapy product.

With the subretinal injection, there is also a potential risk, although rare, for developing sympathetic ophthalmia following subsequent injections into the contralateral eye (or the same eye). Since an immune response takes time to develop, timing the contralateral subretinal eye administration following the injection of the first eye is important. The concern of AAV vector-related immunogenicity and the safety concerns with contralateral (second) eye or repeat administration were extensively discussed at the FDA CTGTAC Meeting on June 29, 2011. To reduce the potential risk, Study 301 was designed to deliver the product to the second eye within eighteen days [12 days ± 6 days] following the product administration into the first eye. More details of the clinical studies are discussed below.

## 4 CLINICAL DEVELOPMENT

The clinical studies that support the BLA include a Phase 1 study with two clinical protocols (Study 101, Study 102) and a Phase 3 study (Study 301) with an extended long-term follow-up (LTFU) for a total of 15 years.

### 4. 1 Phase 1 Studies - Study 101 and Study 102

#### 4.1.1 Study Design

Study 101 was an open-label, dose-exploration safety study in which twelve (12) subjects received unilateral subretinal injection of voretigene neparvovec (first-treated eyes). In Study 102, 11 of the 12 treated Study 101 subjects subsequently received a subretinal injection of voretigene neparvovec in the contralateral eye (second-treated eyes). One of the 12 subjects in Study 101 was not treated in the second eye because of elevated intraocular pressure, an exclusion criterion. The interval between the first- and second-eye injections ranged from 1.7 to 4.6 years. The study duration of both Study 101 and 102 was one year, with extended long-term follow-up (LTFU) planned for a total of 15-years.
4.1.2 Study Objectives

The primary objective of Study 101 was to evaluate the safety and tolerability of three different doses of voretigene neparvovec administered by subretinal injection. The secondary objective was to assess the preliminary efficacy, including visual acuity and visual fields.

4.1.3 Key Enrollment Criteria

Inclusion Criteria
- Eight years of age or older
- Diagnosis of LCA2 due to confirmed RPE65 mutation(s) in both alleles
- Visual acuity no better than (≤) 20/160 (Log MAR 0.9) or visual field less than (<) 20 degrees (20°)

Exclusion Criteria
- 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
- Neutralizing antibodies to AAV2 > 1:1000
- Pre-existing eye conditions that would preclude the planned surgery or interfere with the interpretation of study endpoints (e.g., glaucoma, corneal or lenticular opacities)
- Ocular surgery within previous six months

4.1.4 Treatment Plan

Dose Regimen
The dose of voretigene neparvovec was defined based on the vector genome (vg) and subretinal injection volume (microliter (µL)). Three dose levels (1.5x10¹⁰ vg / 150µL, 4.8x10¹⁰ vg / 150µL, and 1.5x10¹¹ vg / 300 µL), were used for the first-eye injection in Study 101. There was no clear dose effect with respect to bioactivity or preliminary efficacy. For the second-eye injection in Study 102, the Applicant chose the highest dose (1.5x10¹¹ vg / 300 µL) that seemed to be safe in Study 101.

Appendix 1 provides a detailed description of the subretinal injection procedure.

Concomitant Use of Prednisone
Prednisone was given orally at 1mg/kg/day (maximum dose of 60 mg/day) starting 3 days prior to injection and continued for a total of 10 days, followed by 0.5 mg/kg/day for an additional 7 days.

4.1.5 Study Assessments

Safety assessments included routine physical exams and ophthalmic evaluations, adverse event recording, measurements of antibodies to AAV and RPE65 protein, Interferon-γ responses to AAV2 and RPE65 by an enzyme-linked immunospot Assay (ELISPOT) in peripheral blood
mononuclear cells (PBMC), and routine laboratory tests, such as serum chemistries and hematology.

The preliminary bioactivity and efficacy were assessed by visual acuity and visual field testing, electroretinography, contrast sensitivity, color vision testing, pupillary light reflex response, and mobility testing that was in the process of being developed to become the multi-luminance mobility testing (MLMT).

4.2 Phase 3 Study – Study 301

4.2.1 Study Design

Study 301 was an open-label, randomized study. Thirty-one (31) subjects were randomized in a 2:1 ratio to the treatment (n=21) or control (n=10) group. Twenty (20) subjects in the treatment group received subretinal injections of voretigene neparvovec in both eyes. The injection interval between the two eyes of each subject varied from 6 days to 18 days (12 ± 6 days). Subjects who were assigned to the control group did not receive any intervention, including voretigene neparvovec, sham injection, or prednisone. However, control group subjects underwent the same efficacy outcome assessments, including MLMT, as subjects in the treatment group. The study duration was one year.

After the one-year evaluation, nine (9) of the 10 subjects in the Study 301 control group crossed over to receive sequential subretinal injections of voretigene neparvovec to each eye. The injection interval between the two eyes of each subject varied from 7 days to 21 days (14 ± 7 days). The Applicant refers to this part of the study as “Study 302”. The Phase 3 study design is shown in Figure 3.
4.2.2 Study Objective

The objectives of the study were to assess the safety, tolerability and efficacy of sequential
(non-simultaneous) subretinal administration of voretigene neparvovec to each eye.

The primary efficacy objective was to determine whether sequential subretinal administration of
voretigene neparvovec to each eye could improve the subjects’ ability to navigate a course with
obstacles.

4.2.3 Key Enrollment Criteria

Inclusion Criteria
- 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 multi-luminance mobility testing (MLMT), but unable to pass the MLMT
at 1 lux, the lowest luminance level tested

Exclusion Criteria
- 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
4.2.4 Treatment Plan for Subjects in the Treatment Group

Dose Regimen
One dose, $1.5 \times 10^{11}$ vg/300 µL, was given by subretinal injection. Detailed description of the subretinal injection procedure is provided in Appendix 1.

Concomitant Use of Prednisone
Prednisone was given orally at 1 mg/kg/day (a maximum dose of 40 mg/day) starting 3 days before the first-eye injection and continued for a total of 7 days. The prednisone dose was then decreased to 0.5 mg/kg/day (a maximum dose of 20 mg/day) for 5 days, followed by 0.5 mg/kg/every other day until three days prior to the second-eye injection.

The oral prednisone regimen used concomitantly with the second-eye injection was the same as the regimen for the first-eye injection.

4.2.5 Study Assessments

The key efficacy assessments included:
- Performance on the MLMT with one eye patched, then the other eye patched, and then with the use of both eyes;
- Full-field light sensitivity threshold testing using white light to probe potential differential effects on rod versus cone photoreceptors in each eye;
- Best-corrected visual acuity (BCVA) testing on the first eye and then the second eye using the scale adapted from Holladay (Holladay 2004) to assign values for off-chart visual acuities.

Safety assessments included adverse event recording, routine physical exams and ophthalmic evaluations, immune responses to AAV2 and RPE65 (e.g., antibodies to AAV and RPE65, Interferon-γ responses to AAV2 and RPE65 by ELISPOT assay in PBMCs), and routine laboratory tests such as serum chemistries and hematology.

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

- Course layout: There were a total of twelve different course configurations. Each course layout featured the same number of arrows, turns, and obstacles. Course configuration was changed before each test, and the order of course presentation to subjects was randomized before each test. The path for the subject to follow was indicated with standardized black arrows on a white background on the floor.

- Lighting condition: MLMT was conducted using the following seven specified light levels: 1, 4, 10, 50, 125, 250 and 400 lux. The light levels were measured in lux within 20% error. The light levels were verified with calibrated light meters at 5 different
positions on the course. The corresponding real-world conditions ranged from moonless summer night (1 Lux) to office environment (400 Lux).

- MLMT performance: The MLMT was performed at Baseline, Days 30, 90, 180 and 365 using the first eye, the second 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.

- MLMT evaluation and scoring: 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 passing score for each test was based on the lowest light level at which the subject was able to successfully navigate the MLMT course. The difference between the MLMT score at baseline and the MLMT score at a follow-up visit was referred to as the MLMT score change.

Each light level evaluated in the study was assigned a score (i.e., MLMT score), as indicated in Table 2.

<table>
<thead>
<tr>
<th>Lux</th>
<th>1</th>
<th>4</th>
<th>10</th>
<th>50</th>
<th>125</th>
<th>250</th>
<th>400</th>
<th>&gt;400*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score code</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>-1</td>
</tr>
</tbody>
</table>

Note: * Does not pass at 400 lux.
Source: Modified form 9.4.5 Change Score Determination; Mobility Test Validation Study: single-center observational study comparing the performance of normal-sighted and visually-impaired subjects on standardized obstacle courses

Validation of MLMT
To validate this novel primary endpoint, the Applicant conducted a prospective, observational mobility testing validation study in 60 subjects (including 29 subjects with normal vision and 31 subjects with visual impairment) aged 4 through 39 years. Subjects navigated MLMT courses 3 times over a year. At each visit, subjects completed testing using individual eyes, and both eyes, at up to 9 standardized, increasing light levels (ranging from 1 to 400 lux). Accuracy and speed were evaluated, and compared with visual acuity (VA) and visual field (VF). The results showed that:

- MLMT distinguished subjects with normal vision from subjects with visual impairment. Subjects with normal vision passed MLMT on both time and accuracy at all light levels,
while subjects with visual impairment showed a wide range of failing and passing performances:

- The inter-reader agreement of “final pass/fail” of MLMT, which was used to determine the MLMT score change, was 97.9%;

- In subjects with normal vision, visual acuity and MLMT performance accuracy were tightly clustered. Visually impaired subjects with visual acuity loss of 0.5 LogMAR units (or 20/63 Snellen equivalent) or less had accuracy similar to subjects with normal vision in performing MLMT. Conversely, visually impaired subjects who had visual acuity loss greater than 0.5 LogMAR units showed a range of MLMT performance accuracy. Those with greater than 2 LogMAR units loss had poor MLMT performance accuracy. Among visually impaired subjects, the correlation of average accuracy score with mean VA ranged from 0.75 to 0.86 across all visits and eyes.

- Among the visually impaired subjects, correlations between mean accuracy score and sum total degrees (the outcome measure for Goldmann visual field) for each eye/visit combination ranged from -0.37 to -0.53, indicating a weak to moderate correlation.

- The Agency is not aware of any data which correlates the MLMT with activities of daily living beyond those incorporated in the mobility maze.

4.2.6 Efficacy Endpoints

The applicant defined the primary efficacy endpoint for Study 301 as the mean MLMT score change using both eyes from baseline to one year after voretigene neparvovec administration.

The secondary endpoints included:

- Change in full-field light sensitivity threshold testing (FST) using white light, as measured by the first-eye FST, the second-eye FST, and the averaged FST

- MLMT score change using the first eye from baseline to one year

- Change in VA using the first eye, the second eye, and the averaged change in VA of the two eyes

The MLMT score when both eyes are used in testing is almost always a representation of the better seeing eye. Consequently, with an endpoint using both eyes, a subject could have improvement in one treated eye, lose all sight in the other treated eye, and still be considered to have successfully improved following treatment. This concern led FDA to recommend co-primary efficacy endpoints, i.e., MLMT score change using both eyes and MLMT score change using the first eye. However, Study 301 was designed with a single primary endpoint, an MLMT score change using both eyes.
As with all measures of visual function, there are potential limitations in MLMT due to both a floor and ceiling of the measure. Subjects who entered into the trial, who could not complete the course at the highest level of luminance > 400 lux, did not successfully complete the course at subsequent visits, regardless of treatment course. The 400 lux light level was the highest available light level that could be reproducibly provided to the test area, but compared to daylight, it is a low level of light.

There is also a ceiling score. Subjects, who entered the trial at the second lowest level (4 lux) and showed improvement, were only recorded as improving by one unit because they had reached the highest level on the scale.

5 EFFICACY

The primary efficacy analysis was based on 31 subjects who were enrolled in Study 301.

5.1 Study Population

5.1.1 Subject Disposition

Thirty-one (31) subjects were randomized in a 2:1 ratio to the treatment group (n=21) or the control group (n=10). One subject in the treatment group did not receive voretigene neparvovec due to severe retinal atrophy, and one subject in the control group withdrew consent.

Table 3. Subject Disposition in Study 301

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatment Group (n)</th>
<th>Control Group (n)</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>21</td>
<td>10</td>
<td>31</td>
</tr>
<tr>
<td>ITT* population</td>
<td>21</td>
<td>10</td>
<td>31</td>
</tr>
<tr>
<td>mITT** population</td>
<td>20</td>
<td>9</td>
<td>29</td>
</tr>
<tr>
<td>Completed study with one-year assessment</td>
<td>20</td>
<td>9</td>
<td>29</td>
</tr>
<tr>
<td>Discontinued before intervention</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Withdrawal of consent</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Physician decision (severe retinal atrophy)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Crossover to treatment group after one-year</td>
<td>Not Applicable</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Injected in both eyes</td>
<td>20</td>
<td>9</td>
<td>29</td>
</tr>
</tbody>
</table>

Note: ITT*: intention–to-treat population, used for all primary analyses; mITT**: modified intention-to-treat population, used for sensitivity and supportive analyses. Source: Modified based on Table 10.2 in Clinical Study Report: AAV2-hRPEv2-301
5.1.2 Demographics and Baseline Characteristics
The study demographics are summarized in Table 4. Study subjects ranged from 4 to 44 years of age. Twenty (20) subjects were under 18 years of age (20/31, 64%). Overall, the baseline demographics of the two study groups were balanced, except that the treatment group had more pediatric subjects.

Table 4. Demographics of Subjects in Study 301 (ITT)

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatment Group (n=21)</th>
<th>Control Group (n=10)</th>
<th>Total (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>14.7 (11.8)</td>
<td>15.9 (9.5)</td>
<td>15.1 (10.9)</td>
</tr>
<tr>
<td>Range (min, Max)</td>
<td>4, 44</td>
<td>4, 31</td>
<td>4, 44</td>
</tr>
<tr>
<td><strong>Age Groups (Years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-17</td>
<td>15 (75%)</td>
<td>5 (50%)</td>
<td>20 (64%)</td>
</tr>
<tr>
<td>4-10</td>
<td>9 (42%)</td>
<td>5 (50%)</td>
<td>14 (45%)</td>
</tr>
<tr>
<td>11-17</td>
<td>6 (29%)</td>
<td>0</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>≥18</td>
<td>6 (29%)</td>
<td>5 (50%)</td>
<td>11 (36%)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>9 (43%)</td>
<td>4 (40%)</td>
<td>13 (42%)</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>12 (57%)</td>
<td>6 (60%)</td>
<td>18 (58%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>14 (66%)</td>
<td>7 (70%)</td>
<td>21 (68%)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (14%)</td>
<td>2 (20%)</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>American Indian or Alaska</td>
<td>2 (10%)</td>
<td>1 (10%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Native</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>2 (10%)</td>
<td>0</td>
<td>2 (6%)</td>
</tr>
</tbody>
</table>

Source: modified based on Table 10.2 and Table 11.2 in Clinical Study Report: AAV2-hRPEv2-301

5.2 MLMT Score Change Using Both Eyes
Figure 4 depicts 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 the intent-to-treat (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 4. MLMT Score Change Using Both Eyes

Box-plot (above) explanation: lower horizontal line of box is the 25th percentile (1st quartile); upper horizontal line of box is the 75th percentile (3rd quartile); horizontal bar within box is the median; the box represents the middle 50% of MLMT score change distribution. The lower horizontal bar outside box is the minimum, upper horizontal bar outside box is the maximum. Vertical whiskers (dashed lines) indicate the range of values. Dots within box represent the mean.

Source: FDA Statistical Review
Table 5 presents a summary of the MLMT score change using both eyes at one year compared to baseline for the ITT population.

Table 5. MLMT Score Change Using Both Eyes at One Year Compared to Baseline (ITT)

<table>
<thead>
<tr>
<th>MLMT Score Change</th>
<th>Treatment Group (N=21)</th>
<th>Control Group (N=10)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>1.8 (1.1)</td>
<td>0.2 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Range (min, max)</td>
<td>0, 4</td>
<td>-1, 2</td>
<td></td>
</tr>
</tbody>
</table>

*The two-sided p-value is calculated based on Wilcoxon rank-sum test using an exact method.

Source: Modified Table 2.7.3.9 in 2.7.3. Summary of Clinical Efficacy

Table 6 displays the MLMT score change using both eyes in the treatment and control groups. Eleven (11) subjects (11/21, 52%) in the treatment group had an MLMT score change of 2 or more. Only one subject (1/10, 10%) in the control group had an MLMT score change of 2, and no subject in the control group had an MLMT score change greater than 2.

Table 6. MLMT Score Change Using Both Eyes (ITT) at One Year

<table>
<thead>
<tr>
<th>MLMT Score Change</th>
<th>Treatment (n=21)</th>
<th>Control (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: FDA Statistical Review

Figure 5 summarizes the MLMT score using both eyes at baseline and one year for each subject. The top section displays the MLMT score for the subjects (n=21) in the treatment group. The bottom section displays the MLMT score for the subjects (n=10) in the control group. The subjects with an MLMT score -1 did not pass the MLMT at the 400-Lux light level.
Figure 5. MLMT Score Using Both Eyes at Baseline and One Year for Individual Subjects (ITT)

*: One subject in the treatment group did not receive voretigene neparvovec; one subject in the control group withdrew consent.
Score change is displayed next to the Year 1 MLMT score.
Source: FDA Statistical Review.
5.3 MLMT Score Change Using Both Eyes in the Subjects Who were Crossed Over to Receive voretigene neparvovec (Study 302)

After the one-year evaluation, nine (9) of the 10 subjects in the control group were crossed over to receive subretinal injection of voretigene neparvovec into both eyes. The injection interval between the two eyes of each subject varied from 7 days to 21 days (14 ± 7 days).

Figure 6 shows the MLMT score change for the nine (9) subjects in Study 302. A median MLMT score change of 2 for the 9 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 in Study 301 was maintained throughout the 1-year follow-up period.

![Figure 6. MLMT Score Change Using Both Eyes for Subjects in the Treatment and Control Groups in Study 301 and Study 302](image)

Box-plot (above) explanation: lower horizontal line of box is the 25th percentile (1st quartile); upper horizontal line of box is the 75th percentile (3rd quartile); horizontal bar within box is the median; the box represents the middle 50% of MLMT score change distribution. The lower horizontal bar outside box is the minimum, upper horizontal bar outside box is the maximum. Vertical whiskers (dashed lines) indicate the range of values. Dots within box represent the mean.

Source: FDA Statistical Review
5.4 MLMT Score Change Using First-treated Eye

The box plots in Figure 7 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. The location test based on a Wilcoxon Rank-Sum test showed a statistically significant difference at the one-year 1 follow-up visit in the MLMT score change between the two groups (p-value < 0.001).

Figure 7. MLMT Score Change Using the First Eye

Box-plot (above) explanation: lower horizontal line of box is the 25th percentile (1st quartile); upper horizontal line of box is the 75th percentile (3rd quartile); horizontal bar within box is the median; the box represents the middle 50% of MLMT score change distribution. The lower horizontal bar outside box is the minimum, upper horizontal bar outside box is the maximum. Vertical whiskers (dashed lines) indicate the range of values. Dots within box represent the mean.

Source: FDA Statistical Review
Table 7 displays MLMT score change using the first and second eyes. Using the first-treated eye, 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 2 using respective control eyes. Similar results were observed on MLMT score change using the second-treated eyes in the treatment group and respective eyes in the control group.

Table 7. MLMT Score Change Using One Eye at One Year

<table>
<thead>
<tr>
<th>Change Score</th>
<th>First-treated Eye (N=21)</th>
<th>Control (N=10)</th>
<th>Second-treated Eye (N=21)</th>
<th>Control (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>0</td>
<td>4</td>
<td>6</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: FDA Statistical Review

Figure 8 summarizes the MLMT score using the first eye at baseline and one year for each subject. The top section displays the MLMT score for the subjects (n=21) using the first-treated eye in the treatment group. The bottom section displays the MLMT score for the subjects (n=10) using the corresponding untreated-first eye in the control group. The subjects with an MLMT score of -1 did not pass the MLMT at the 400-Lux light level. These subjects did not have any improvement in the MLMT, which suggests that subjects with more advanced disease may be less likely to improve with voretigene neparvovec.
Figure 8. MLMT Score Using First Eye at Baseline and Year 1 for Individual Subjects (ITT)

*: One subject in the treatment group did not receive voretigene neparvovec; one subject in the control group withdrew consent.

Score change is displayed next to the Year 1 MLMT score.

Source: FDA Statistical Review
5.5 Other Secondary Efficacy Endpoints

Table 8 shows the results of other secondary endpoints in Study 301.

Table 8. Other Secondary Efficacy Endpoints in Study 301

<table>
<thead>
<tr>
<th>Key Secondary (ITT)</th>
<th>Difference (95% CI) Treatment-control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FST White Light first-treated eye</td>
<td>-2.33 (-3.44, -1.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FST White Light second-treated eye</td>
<td>-1.89 (-3.03, -0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VA (Holladay, LogMAR) first-treated eye</td>
<td>-0.14 (-0.53, 0.25)</td>
<td>0.46</td>
</tr>
<tr>
<td>VA (Holladay, LogMAR) second-treated eye</td>
<td>-0.13 (-0.28, 0.01)</td>
<td>0.072</td>
</tr>
</tbody>
</table>

Negative change represents improvement in Full Field Stimulus Threshold (FST). Negative change represents improvement in Visual Acuity (VA).

Source: Modified Table 2.5.1, Module 2.5: Clinical Overview

**Full Field Stimulus Threshold (FST)**
A statistically significant difference in FST, comparing the treatment and control groups, in the first-treated eye as well as the second-treated eye (Table 8) was noted. However, the clinical correlation of FST is unclear, and FST results are susceptible to bias in this unmasked trial.

**Visual Acuity (VA)**
Table 9 compares the VA change between the treatment and control groups in Study 301 at one year after voretigene neparvovec administration. Improvement of LogMAR 0.3 ($\leq -\text{LogMAR} 0.3$) is considered clinically meaningful (equivalent to a halving of the visual angle, e.g. 20/80 to 20/40).

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 eye. However, the mean VA changes did not show a statistically significant difference between the treatment and control groups for either the first- or the second-treated eyes over the duration of the study, as shown in Table 8.

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 (7) subjects in the first-treated eye and three (3) subjects in the second-treated eye. Among the 9 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 (4) subjects in the first-treated eye and no subjects in the second-treated eye.
Table 9. VA Improvement of LogMAR 0.3 in Treatment and Control Groups (Study 301) at One Year *

<table>
<thead>
<tr>
<th>Study 301</th>
<th>VA Improvement of LogMAR 0.3 In the First Eye N (%)</th>
<th>VA Improvement of LogMAR 0.3 In the Second Eye N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Group (n=20)</td>
<td>11 (11/20, 55%)</td>
<td>4 (4/20, 20%)</td>
</tr>
<tr>
<td>MLMT score change ≥ 2 (n=11)</td>
<td>7 (7/11, 64%)</td>
<td>4 (4/11, 36%)</td>
</tr>
<tr>
<td>MLMT score change &lt; 2 (n=9)</td>
<td>4 (4/9, 44%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Control Group (n=9)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*as two subjects withdrew directly after randomization, VA was assessed in the mITT population for this exploratory endpoint.

Source: FDA statistical and clinical review

5.6 Efficacy Conclusion:

The primary efficacy analysis was based on 31 subjects in Study 301. At the one-year evaluation, an MLMT score change of 2 or more occurred in eleven (11) of the 21 (11/21, 52%) subjects using both-treated eyes and fifteen (15) of the 21 (15/21, 71%) subjects using the first-treated eye. The median MLMT score change was significantly different between the treatment and control groups (p-value=0.001 for using both eyes; p-value < 0.001 for using the first eye). The median MLMT score change of 2, using both treated eyes, for the subjects in the treatment group (n=20) was maintained throughout the 1-year follow-up period. However, it is unclear if the effect decays over time, as longer term follow up data is not available. In addition, a median MLMT score change of 2, using both treated eyes, occurred in the nine (9) subjects who crossed over from the control group to the treatment group in Study 302. Individuals with more advanced disease did not demonstrate any improvement in MLMT over the course of the study, suggesting that perhaps patients with advanced disease may be less likely to benefit, despite the limitations of MLMT.

At one year, a 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 a VA improvement of LogMAR 0.3 in either the first eye or the second eye. However, the mean VA changes were not significantly different between the treatment and control groups, for either the first- or the second-treated eyes over the duration of the study (p-value=0.46 for the first-treated eye; p-value=0.072 for the second-treated eye).
6 SAFETY

6.1 Study Population

The safety analysis was based on 41 subjects (81 injected eyes) who were enrolled in Phase 1 and Phase 3 studies, as detailed in Table 10.

Table 10. Subjects Who Received Subretinal Injection of Voretigene Neparvovec

<table>
<thead>
<tr>
<th>Study 101 (first eye)</th>
<th>1.5 x10^10 vg 150 µL</th>
<th>4.8 x10^10 vg 150 µL</th>
<th>1.5x10^11 vg 300 µL</th>
<th>Total subjects</th>
<th>Total eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 102 (second eye)</td>
<td>-</td>
<td>-</td>
<td>11^a</td>
<td>11^a</td>
<td>11^a</td>
</tr>
<tr>
<td>Study 301 intervention (both eyes)</td>
<td>-</td>
<td>-</td>
<td>20^b</td>
<td>20^b</td>
<td>40</td>
</tr>
<tr>
<td>Study 302 (cross-over to treat both eyes)</td>
<td>-</td>
<td>-</td>
<td>9</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>41 subjects</td>
<td>81 eyes</td>
</tr>
</tbody>
</table>

^a One subject was not eligible for Study 102 due to elevated intraocular pressure; this subject’s second eye did not receive voretigene neparvovec.

^b One subject in the treatment group did not receive voretigene neparvovec; one subject in the control group withdrew consent.

Source: Modified based Table 2.7.4.2 Module 2.7.4. Clinical Summary of Safety
The demographics of the safety population are shown in Table 11. The subjects ranged from 4 to 44 years old. Twenty-five (25/41, 61%) subjects were under 18 years of age.

Table 11. Demographics of the Safety Population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study 101 (n=12)</th>
<th>Study 301 Treatment Group (n=20)</th>
<th>Study 301 Control Group (n=9)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), N, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>20.8 (11.2)</td>
<td>14.6 (12)</td>
<td>15.2 (8.3%)</td>
<td>16.6 (11.1)</td>
</tr>
<tr>
<td>Range</td>
<td>8, 44</td>
<td>4, 44</td>
<td>5, 29</td>
<td>4, 44</td>
</tr>
<tr>
<td>Pediatric (&lt;18)</td>
<td>5 (42%)</td>
<td>15 (75%)</td>
<td>5 (50%)</td>
<td>25 (61%)</td>
</tr>
<tr>
<td>Adults (&gt;18)</td>
<td>7 (58%)</td>
<td>5 (25%)</td>
<td>4 (44%)</td>
<td>16 (39%)</td>
</tr>
<tr>
<td>Gender, N, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (58%)</td>
<td>8 (40%)</td>
<td>3 (33%)</td>
<td>18 (44%)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (42%)</td>
<td>12 (60%)</td>
<td>6 (67%)</td>
<td>23 (56%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>11 (92%)</td>
<td>14 (70%)</td>
<td>6 (67%)</td>
<td>31 (76%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (8%)</td>
<td>2 (10%)</td>
<td>2 (22%)</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>American Indian or</td>
<td>0</td>
<td>2 (10%)</td>
<td>1 (11%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Alaska Native</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African</td>
<td>0</td>
<td>2 (10%)</td>
<td>0</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>American</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>0</td>
<td>5 (25%)</td>
<td>1 (11%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>12 (100%)</td>
<td>15 (75%)</td>
<td>8 (89%)</td>
<td>35 (85%)</td>
</tr>
</tbody>
</table>

Source: Modified based on Table 2.7.4.3, Module 2.7.4: Clinical Summary of Safety

6.2 Adverse Events (AEs)

In the clinical studies, different subjects received voretigene neparvovec at different time points; therefore, parallel comparison of rates of AEs is not always possible, especially since there was no intervention (e.g., there were no sham injections) in the control group. All AEs presented in this safety analysis are considered to be related to: voretigene neparvovec, the subretinal injection procedure, or the concomitant use of corticosteroids.

6.2.1 Ocular Adverse Events

Thirty (30) (30/41, 73%) subjects in the clinical studies had ocular AEs that involved 51 injected eyes (51/81, 63%). Table 12 lists the incidence of each ocular AE.
Table 12. Ocular Adverse Events

<table>
<thead>
<tr>
<th>Ocular AEs</th>
<th>Subjects (n=41)</th>
<th>Treated Eyes (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ocular AE</td>
<td>30 (73%)</td>
<td>51 (63%)</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>9 (22%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>Intraocular pressure (IOP) increased</td>
<td>8 (20%)</td>
<td>10 (12%)</td>
</tr>
<tr>
<td>Cataract development*</td>
<td>7 (17%)</td>
<td>11 (14%)</td>
</tr>
<tr>
<td>Retinal tear</td>
<td>4 (10%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>4 (10%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Corneal dellen</td>
<td>3 (7%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Eye Inflammation</td>
<td>3 (7%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Subretinal deposits</td>
<td>3 (7%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>3 (7%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Macular hole</td>
<td>3 (7%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Maculopathy (including macular pucker)</td>
<td>2 (5%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Foveal thinning and loss of foveal function</td>
<td>1 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Retinal hemorrhage</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Fovea dehiscence</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

*Cataract development includes both extracted and unextracted cataracts

Source: Modified based on Table 2.7.4.9, Module 2.7.4: Clinical Summary of Safety

Intraocular Pressure (IOP) increased
Increased IOP was noted in 10 of 81 (12%) injected eyes of eight (8) subjects. Increased IOP was successfully treated with topical medications in all but one eye. One case of elevated IOP resulted in optic atrophy with permanent visual loss. This is listed as a serious adverse event (SAE) in Table 13.

Cataract
Among the 81 eyes that received voretigene neparvovec, eleven (11) eyes (14%) of seven (7) subjects had documented progression of existing cataract or formation of new cataract. Three subjects had their cataract successfully extracted. Other cataract cases have not received elective extraction procedures.

Retinal Tears
Four of the 81 (5%) eyes that received voretigene neparvovec had a retinal tear noted during the administration procedure. Retinal tears were observed and repaired by the surgeon with laser retinalpexy during the subretinal injection procedure. None of the tears developed into retinal detachments.
Macular/Retinal Hole
One subject in Study 101 developed an asymptomatic macular hole two weeks after subretinal administration of voretigene neparvovec. The surgical procedure protocol was modified afterward to include the use of Perfluoron, a liquid agent used to facilitate retinal flattening and anterior displacement of subretinal fluid.

One subject had a full thickness macular hole in the first-treated eye, ten days following subretinal administration of voretigene neparvovec. By Day 30, the macular hole had improved. At the same time, macular thinning was noted and a diagnosis of macular degeneration was made. The macular thinning was not noted to progress during the trial.

One subject had an operculated retinal hole at the post-injection Day 14 visit. A retinal detachment did not subsequently occur.

6.2.2 Serious Adverse Events (SAEs) Reports with Permanent Visual Loss

Table 13 summarizes the two SAEs that occurred following the subretinal injection of voretigene neparvovec.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age, gender</th>
<th>Study</th>
<th>Events</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| 1       | 21 year old, male | 102*   | • Endophthalmitis at Week 4; vitreous culture positive for Staphylococcus epidermidis, treated with anti-infective drugs and periocular steroids  
• Elevated IOP between Days 90 - 180 due to periocular steroids  
• Optic nerve cupping right eye on Day 172; trabeculectomy done  
• Cataract following trabeculectomy; cataract extracted at Day 189 | Irreversible optic atrophy due to sustained increased IOP |
| 2       | 19-year old, female | 302**  | • Bleb elevated the fovea in both eyes  
• Decreased central vision at Day 30  
• Foveal thinning in both eyes at Days 30 & 90 (left: 157 to 70; right: 256 to 102)  
• Visual acuity continues to drop from Day 30 to Day 90  
• Improved retinal sensitivity  
• No recovery of central vision at Year 1 | Permanent loss of central vision in the right eye from 20/150 at baseline down to 20/320 |

Note: *the second eye received intervention; **subject was randomized to control group in Study 301 and received product a year later

Source: 2.7.4.2.3: Narratives from Module 2.7.4: Clinical Summary of Safety)
6.2.3 Systemic Adverse Events

Systemic adverse events included leukocytosis (17/41, 41%), fever (17/41, 41%), nausea (14/41, 34%), and vomiting (13/41, 32%). Leukocytosis resolved after the corticosteroid treatment courses were completed. Fever, nausea, and vomiting were treated symptomatically.

6.3 Safety Summary

Of the 41 subjects, 30 subjects reported ocular AEs that involved 51 injected eyes (51/81, 63%) following the subretinal injection of voretigene neparvovec. The more serious ocular AEs, including endophthalmitis, macular holes, foveal dehiscence, retinal hemorrhage, retinal tears, elevated intraocular pressure, and cataract development, might have long-term consequences, especially if they were left untreated.

6.4 Immunogenicity

To minimize the immune responses to voretigene neparvovec, oral prednisone was given surrounding the time of voretigene neparvovec administration (detailed treatment regimen is described in Sections 4.1.4 and 4.2.4). To monitor the immunologic responses to voretigene neparvovec, the following tests were performed at Baseline, and at Days 30, 90, and 365 after voretigene neparvovec administration:

- Anti-AAV2 antibody and RPE65-specific antibody in serum samples by Enzyme-Linked Immunosorbert Assay (ELISA)
- Interferon-γ Responses to AAV2 and RPE65 by an Enzyme-Linked Immunospot Assay (ELISPOT) in peripheral blood mononuclear cells (PBMC)

As summarized in Table 14 and Table 15, in the setting of concomitant prednisone use, the extent of immune response to AAV capsid and RPE65 is limited.

**Table 14. Assessment of Humoral Immune Response**

<table>
<thead>
<tr>
<th>Tests</th>
<th>Study 101 (n=12)</th>
<th>Study 102 (n=11)</th>
<th>Study 301 (n=21)</th>
<th>Study 302 (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-AAV2 antibody and RPE65-specific antibody in serum samples by ELISA at BL, Days 14, 30, and 90, and Year 1</td>
<td>Minimal or no sustained increase in antibody titers to AAV2 capsid and RPE</td>
<td>Minimal or no change in antibody titers to AAV capsid and RPE65</td>
<td>Minimal or no changes in antibody titers to AAV capsid and RPE65</td>
<td>Rise in antibody titer to AAV2 capsid in six subjects who had low titer at baseline, but no clear clinical correlation</td>
</tr>
</tbody>
</table>

BL: Baseline
Source: Section 2.7.4.4 Cell-mediated and humoral immune responses with modification
Table 15 Assessment of T-cell Immune Responses

<table>
<thead>
<tr>
<th>Tests</th>
<th>Study 101 (n=12)</th>
<th>Study 102 (n=11)</th>
<th>Study 301 (n=21)</th>
<th>Study 302 (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human PBMC Interferon-γ Responses to AAV2 and RPE65 by ELISPOT at BL, Days 14, 30, and 90</td>
<td>No T cell response to AAV capsid and RPE65</td>
<td>Six subjects with low response at single time point</td>
<td>Two subjects with low response at single time point and one subject with medium response at single time point</td>
<td>Three subjects with low response(^{(a)}), 1 subject with medium response(^{(b)}), and 1 subject with high response(^{(c)})</td>
</tr>
</tbody>
</table>

(a) Two subject: low response at single time point (Year 1C). One subject low response at two time points (Year 1C, Day 30B). Year 1C time point is baseline, i.e. prior to vector injection.

(b) One subject: medium response at single time point (at Baseline, Year 1C)

(c) One subject: high response at two time points (Day 30B and 90B). The same subject had medium responses at Baseline, Year 1C.

Source: Section 2.7.4.4 Cell-mediated and humoral immune response with modification
7 QUESTIONS FOR THE ADVISORY COMMITTEE

Discussion Question 1

The primary efficacy endpoint of Study 301 was improvement in MLMT. At the one-year evaluation, eleven (11) of the 21 (11/21, 52%) subjects using both-treated eyes and fifteen (15) of the 21 (15/21, 71%) subjects using the first-treated eye had 2-light level or more improvement in MLMT (i.e., an MLMT score improvement of ≥2). The difference in the median MLMT score change between the treatment and control groups is statistically significant.

FDA review of this BLA identified the following issues regarding the use of MLMT to assess the functional vision, including:

- The limited data on this novel outcome measure; and
- The relationship of the MLMT score change to activities of daily living

Please discuss whether a 2-light level improvement in MLMT is clinically meaningful in “patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy.”

Discussion Question 2

Because of the safety concerns related to the subretinal injection procedure, only subjects who had significant vision loss were enrolled into the clinical studies. The youngest subject treated was 4 years old. Additionally, individuals with more advanced disease did not appear to benefit from study agent administration. Considering that patients carrying disease-causing RPE65 mutations would be expected to have progressive vision loss, please discuss the optimal time to treat patients, especially,

a. At what stage of clinical presentation do the benefits of therapy outweigh the risks?

b. How can the data from subjects with advanced vision loss be extrapolated to patients with earlier stages of disease, with or without measurable vision loss prior to treatment?

c. Considering the adverse events associated with the subretinal injection of voretigene neparvovec and the concomitant use of oral prednisone, what are your concerns for treating pediatric patients at a young age?

d. What is the reasonable minimal age, if any, that you would recommend for treatment?
Discussion Question 3

In the clinical studies supporting the BLA, each eye received a one-time subretinal injection of voretigene neparvovec. The median MLMT score change of 2 in the treatment group of Study 301 was observed at the Day 30 visit following voretigene neparvovec administration, and was maintained throughout the 1-year follow-up period. However, there is no available long term follow up data to address whether the effect decays over time. Therefore, the duration of AAV2-mediated transgene expression leading to sustained clinical benefits beyond one year is unclear.

As such, repeat administration of voretigene neparvovec may be indicated to maintain vision or delay vision loss. However, as repeat administration of voretigene neparvovec in any eye was not evaluated in the clinical studies, there are no clinical data addressing potential benefit and risk of re-administration.

a. Please discuss the potential benefits and risks of repeat administration of voretigene neparvovec into one eye.

b. What additional data, if any, would be necessary to support such repeat administration?

Discussion Question 4 (voting question)

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?
8 REFERENCE LIST


Appendix 1 Subretinal Injection

Surgical Procedure: Within 120 minutes prior to surgery, the eye was dilated. Topical anti-infective drops were also applied, followed at least five minutes later by a topical nonsteroidal anti-inflammatory drug to minimize intraoperative miosis. Surgery was performed under general anesthesia supplemented by local (retrobulbar) anesthetic irrigation. The eye was prepped with 5% betadine solution placed in the conjunctival fornix and on the peri-ocular skin and draped under sterile conditions. The product injection apparatus was prepared on the sterile surgical field by attaching a Bausch and Lomb Storz® 39 gauge hydrodissection Retinal Cannula (REF E7365) to the male luer lock end of a 6 inch Eagle Laboratories Fluid Tubing Extension Kit (REF 169-30L-6) and connecting the female end to a 1 mL polycarbonate luer lock BD Syringe (REF 309628), which was loaded with the product by a pharmacist. Voretigene neparvovec was injected through the tubing and the cannula to eliminate any air in the tubing and the volume of the product available for injection was confirmed.

A lid speculum was placed and a standard 3-port pars plana vitrectomy was performed, using 20-gauge instrumentation and visualization with an operating microscope. Conjunctival peritomy incisions were made with Westcott scissors for 120 degrees temporally, and 60 degrees superior nasally. Tenon’s capsule was dissected from the underlying sclera. Episcleral hemostasis was achieved with bipolar cautery. A retrobulbar irrigation of 5 mL 0.5% bupivacaine hydrochloride [without epinephrine] was performed both to mechanically stabilize the globe and to provide postoperative analgesia.

Sclerotomy incisions were made 3.5 millimeters posterior to the corneoscleral limbus in the inferotemporal, superotemporal, and superonasal quadrants. A 7-0 vicryl suture was placed in a vertical mattress configuration surrounding the inferotemporal sclerotomy and used to fixate the flange of the infusion cannula. The tip of the infusion cannula was directly visualized through the pupil to confirm its intravitreal position prior to initiating the infusion of balanced salt solution enriched with bicarbonate, dextrose, and glutathione. Infusion pressure was maintained at 30 mm Hg throughout the procedure, except during the subretinal injection.

Core vitrectomy was performed at high cutting rate (800-2500 cuts per minute) and low suction (80-150 mm Hg) settings. The vitreous was removed as completely as possible with special attention to remove any vitreous in the vicinity of the superior sclerotomy sites to avoid vitreoretinal traction induced by instruments passing into and out of the eye, and to prevent vitreous from occluding the tip of the 39-gauge subretinal injection cannula. After completion of the core vitrectomy, the posterior pole was explored for residual cortical vitreous using a silicone tipped 20-gauge cannula (Alcon/Grieshaber Microsurgical Instruments REF 8065 149520) with direct linear suction at 150 mm Hg. If posterior cortical vitreous was engaged, the hyaloid face was separated from the posterior pole with gentle sweeping motion of the cannula as suction was maintained. A complete posterior vitreous detachment (PVD) was confirmed when a glial ring is released from the optic nerve (Weiss ring) and/or there was no displacement of the silicone cannula by vitreous traction. At this point, the vitreous cortex was no longer attached to the macular area. The remaining vitreous was then removed as completely as possible with the
voretigene neparvovec

vitreous cutting instrument, especially behind the sclerotomy incisions. The macular area was examined for the presence of an epiretinal membrane and if present, the membrane was mobilized with a membrane scraper (DORC-Tano brush, Backflush with brush needle 20G/0.9mm REF 1281.BD), and removed with intraocular forceps (Grieshaber Revolution Dyps 20 gauge ILM forceps REF 707.44).

Prior to subretinal injection of voretigene neparvovec, a volume between 0.1 and 0.5 mL of perfluorooctane liquid (Perfluoron® Liquid, Alcon Laboratories; Ontario, Canada REF 8065900164) was injected over the macula to cover the fovea. The infusion pressure was then reduced to 10 mm Hg in order to accommodate the additional intraocular volume added by the vector injection. The Storz® 39-gauge hydrodissection cannula was placed in the sclerotomy by the surgeon while the assistant handled the syringe containing voretigene neparvovec. The cannula tip was placed on the retina in the area of the papillomacular bundle, superotemporal to the optic nerve and superior to the macular center. The cannula was placed a minimum of 2 mm from the foveal center but posterior to the equator of the eye.

The injection was performed in two steps. First, the hydrodissection cannula was positioned so as to indent the retina and drape the retina over the tip. The surgeon directed the assistant to inject a small amount of voretigene neparvovec to confirm that the tip is not occluded and it was properly positioned. Next, if a bleb was raised, voretigene neparvovec was injected to deliver a total volume of 0.3 mL. If no bleb was created during the test injection, the cannula tip was repositioned and the sequence was repeated. Any voretigene neparvovec injected into the vitreous will be removed by gentle aspiration with the vitreous cutter. At the completion of the injection, the hydrodissection cannula was removed and the infusion pressure was restored to 30 mmHg.

Following subretinal injection of voretigene neparvovec, the retina was inspected with indirect ophthalmoscopy and scleral indentation. Any retinal breaks identified were treated with retinopexy prior to fluid-air exchange. If bleeding was seen at the injection site, intraocular pressure was raised with closed sclerotomy sites until hemostasis was achieved. Fluid-air exchange was performed with a silicone tipped backflow cannula (REF 1281.AD, Dutch Ophthalmic Research Company), carefully avoiding draining through the retinotomy created for the subretinal injection. Perfluoron® Liquid was removed at this time.

The sclerotomy sites were closed. A retrobulbar infusion of 1 mL triamcinolone acetonide solution (40 mg/mL) was delivered followed by conjunctival closure. Subconjunctival injection of 0.5 mL of 4 mg/mL steroid solution and 0.5 mL of anti-infective solution was administered. The ocular surface was dressed with one inch of a steroid/anti-infective ointment and a patch, and eye shield was put in position and secured over the eye which received voretigene neparvovec.

Supine head positioning was instituted in the post-operative period to orient the eye such that the desired macular area of retina-RPE cell treatment was placed in the most dependent position. The subject was maintained in a supine position (or that required for positioning of the air bubble) except for meals and bathroom activity. Position was maintained for 24 hours or until
resorption of the subretinal injection was complete. Ophthalmology examinations were performed daily for three days, followed by Visits at Week 2, Days 30, 60, 180, and Year 1. Source: BLA submission Study 301 protocol