BLA Clinical Review Memorandum

Application Type	BLA
STN	125610
CBER Received Date	Pre-clinical: 4/27/2016 Clinical: 2/22/2017 CMC/final: 5/16/2017
PDUFA Goal Date	1/12/2018
Division / Office	DCEPT/OTAT
Priority Review (Yes/No)	Yes
Reviewer	Yao-Yao Zhu, MD, PhD
Consultants	Wiley A. Chambers, MD (CDER) Bernard P. Lepri, OD, MS, Med (CDRH)
Review Completion Date / Stamped Date	12/16/2017
Supervisory Concurrence	Changting Haudenschild, MD Lei Xu, MD, PhD Tejashri Purohit-Sheth, MD
Applicant	Spark Therapeutics Inc.
Established Name	Voretigene neparvovec
(Proposed) Trade Name	LUXTURNA
Pharmacologic Class	Adeno-associated virus gene therapy vector
Formulation(s), including Adjuvants, etc.	A suspension supplied in a 0.5 mL extractable volume in a 2 mL single-dose vial; the supplied concentration (5×10^{12} vg/mL) requires a 1:10 dilution prior to administration. The diluent is supplied in two single-use 2 mL vials.
Dosage Form(s) and Route(s) of Administration	The recommended dose for each eye is 1.5×10^{11} vector genomes (vg), administered by subretinal injection in a total volume of 0.3 mL.
Dosing Regimen	Administration to each eye should be performed on separate days, at least 6 days apart
Indication(s) and Intended Population(s)	For the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy
Orphan Designated (Yes/No)	Yes

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LIST OF ABBREVIATIONS

AAV	Adeno-associated virus
AAV2-hRPE65v2	AAV serotype 2 carrying the human *RPE65* gene, voretigene neparvovec
AC	Advisory committee
AE	Adverse event
BCVA	Best-corrected visual acuity
BD	Biodistribution
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
CβA	Chicken beta actin
CDC	Center for Disease Control
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CHOP	Children's Hospital of Philadelphia
CLIA	Clinical Laboratory Improvement Amendments
CMC	Chemistry, manufacturing, and controls
CMS	Centers for Medicare and Medicaid Services
CMV	Cytomegalovirus
CSR	Clinical Study Report
CTGTAC	Cellular, Tissue, and Gene Therapies Advisory Committee
dB	Decibels
DCEPT	Division of Clinical Evaluation and Pharmacology/Toxicology
DSMB	Data and Safety Monitoring Board
eCTD	The electronic common technical document
ELISA	Enzyme-Linked Immunosorbent Assay
ELISPOT	The Enzyme-Linked ImmunoSpot
EMA	European Medicines Agency
EOP1	End of Phase 1 (Phase 2, Phase 3)
EOSRD	Early Onset Severe Retinal Dystrophy
ERG	Electroretinogram
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FDAAA	The Food and Drug Administration Amendments Act of 2007
FST	Full-field light sensitivity threshold
GCP	Good Clinical Practices
HDE	Humanitarian Device Exemption
hRPE	Human retinal pigment epithelium
hRPE65	Human retinal pigment epithelium 65 kDa protein
IA	University of Iowa
ICF	Informed consent form
ICH	the International Conference of Harmonization
IEC	Independent Ethics Committee
IND	Investigational new drug application
IOP	Intraocular pressure
IRD	Inherited Retinal Dystrophy
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
LTFU	Long-term follow-up
Lux	SI unit of illumination; one lumen per square meter
Microliter (μL)	A unit of fluid measure being one millionth of a liter
Micron (μM)	a unit of length equal to one millionth of a meter
mITT	Modified intent-to-treat
MLMT	Multi-luminance mobility testing
MTVS	Mobility Test Validation Study
NHP	Non-human primate
NOAEL	The no observed adverse effect level
OCT	Optical coherence tomography
OBE	Office of Biostatistics and Epidemiology
O&M	Orientation and Mobility
OTAT	Office of Tissues and Advanced Therapies
PD	Pharmacodynamics
PDUFA	Prescription Drug User Fee Act
PK	Pharmacokinetics
PMA	Premarket Approval
PBMC	Peripheral blood mononuclear cells
polyA	Polyadenylation
PLR	Pupillary light reflex
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PRO	Patient-reported outcome
QoL	Quality of Life
qPCR	Quantitative polymerase chain reaction
REMS	Risk evaluation and mitigation strategy
RP	Retinitis pigmentosa
RPE	Retinal pigment epithelium
RPE65	Retinal pigment epithelium 65 kDa protein
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SECORD	Severe Early Childhood Onset Retinal Dystrophy
SPA	Special Protocol Assessment
STN	Submission Tracking Number
SUN	Second University of Naples, Italy
TEAE	Treatment emergent adverse event
VA	Visual acuity
VF	Visual field
VFQ	Visual Function Questionnaire
VG	Vector genome

1. EXECUTIVE SUMMARY

Voretigene neparvovec (proprietary name: LUXTURNA) is a recombinant adeno-associated virus serotype 2 (AAV2) expressing the gene for human retinal pigment epithelial 65 kDa protein (*hRPE65*). The proposed indication for voretigene neparvovec is for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy.

BLA 125610 is supported by clinical data from a Phase 1 study and a Phase 3 study conducted under IND 13408. The Phase 3 study provides the primary evidence of effectiveness. Both the Phase 1 and Phase 3 studies contribute to the safety database.

Voretigene neparvovec was granted Orphan Drug designation and Rare Pediatric Disease designation.

The Phase 1 study was an open-label, dose-escalation safety study in a total of 12 subjects with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Eleven of the 12 subjects received subretinal injection of voretigene neparvovec to each eye with an injection interval ranging from 1.7 to 4.6 years.

The Phase 3 study was an open-label, randomized, controlled, and cross-over trial, designed to evaluate efficacy and safety of sequential subretinal injection of voretigene neparvovec to each eye. A total of 31 subjects in two study sites were randomized in a 2:1 ratio to either the treatment group (n=21) or the control group (n=10). The injection interval between the two eyes ranged from 6 to18 days. The subjects who were randomized to the control group were crossed over to receive voretigene neparvovec after one year of observation. The average age was 15 years (4 to 44 years). There were 20 (64%) pediatric subjects. The primary efficacy endpoint was defined as the multi-luminance mobility test (MLMT) score change using both eyes from baseline to Year 1. The MLMT was designed to measure functional vision, namely the ability of a subject to navigate a course accurately and at a reasonable pace at seven levels of environmental illumination.

At Year 1, there was a statistically significant difference in the mean and median MLMT score change using both eyes or the first-treated eye between the treatment and the control groups, favoring the treatment group. A median MLMT score change of 2 (improvement of 2-luminance level) using both eyes or the first-treated eye was observed in the treatment group at Day 30 and sustained throughout the one-year period, while a median MLMT score change of 0 was observed in the control group. An MLMT score change of 2 or greater occurred in 52% of the subjects in the treatment group compared to 10% of the subjects in the control group when using both eyes. An MLMT score change of 2 or greater occurred in 71% of the subjects in the treatment group compared to none in the control group when using individual eyes. An MLMT score change of two or greater is considered a clinically meaningful benefit in functional vision. Results of the secondary endpoints, including full-field light sensitivity threshold (FST) and visual acuity (VA), were supportive for MLMT. The 2-luminance level improvement in MLMT in the treatment group was sustained for two years.

The safety population consisted of 41 subjects (81 treated eyes) enrolled in the Phase 1 and the Phase 3 trials. The average age of the 41 subjects was 17 years ranging from 4 to 44 years. There were 25 (61%) pediatric subjects. Twenty-seven (66%) subjects in the clinical studies had ocular adverse reactions that involved 46 injected eyes (57%). The most common adverse reactions (incidence ≥ 5%) were conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, macular hole, eye inflammation, macular breaks, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula). There were two serious adverse events, endophthalmitis and permanent vision loss. In the setting of systemic corticosteroid use, there was limited humoral or cytotoxic T-cell response to either the AAV2 vector capsid or the transgene product *RPE65*.

There were 25 pediatric subjects in the Phase 1 and Phase 3 studies, including 21 children (age 4 years to less than 12 years) and 4 adolescents (age 12 years to less than 17 years). No significant differences in efficacy or safety were observed between the different pediatric subgroups or between pediatric and adult subgroups in the trial.

A Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) meeting was held on October 12, 2017 to discuss safety and efficacy of voretigene neparvovec. All 16 AC members voted "Yes" to an overall favorable benefit-risk profile of voretigene neparvovec.

The reviewed safety data do not warrant a Risk Evaluation and Mitigation Strategies (REMS), a safety postmarketing requirement (PMR) study, or a safety postmarketing commitment (PMC) study. The postmarketing risk mitigation plans include product labeling, applicant's pharmacy and surgical training, a registry study as well as an ongoing long-term follow-up of the 41 subjects under IND 13408.

In conclusion, biallelic *RPE65* mutation-associated retinal dystrophy is a serious and sight-threatening genetic disorder with an unmet medical need. The Phase 3 study was an adequate and well-controlled investigation, and provided substantial evidence of effectiveness of voretigene neparvovec. Efficacy was based on improvement in multi-luminance mobility testing (MLMT), which was maintained throughout the 2-year follow-up period, and denotes an improvement in functional vision. The more serious risks associated with subretinal administration of voretigene neparvovec and concomitant oral corticosteroid use include endophthalmitis, permanent vision loss, increased intraocular pressure, retinal tears or breaks, and cataract development and/or progression. These risks might have long-term consequences, especially if left untreated. However, these risks can be mitigated by routine medical management, adequate Prescribing Information (PI), and postmarketing plan proposed by the applicant. The efficacy and safety data in the BLA support a favorable benefit-risk profile for patients with biallelic *RPE65* mutation-associated retinal dystrophy. Therefore, the reviewer recommends regular approval of voretigene neparvovec with a recommended dose of 1.5×10^{11} vector genomes (vg) for each eye, administered by subretinal injection in a total volume of 0.3 mL.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

(Section 7.1.2)

As shown in Table 1, the average age of the 31 randomized subjects in the Phase 3 study was 15 years (ranging from 4 to 44 years), including 20 (64%) pediatric subjects (age from 4 to 17 years) and 11 adults. Overall, the baseline demographics of the two study groups were balanced, except that the treatment group had more pediatric subjects.

Subgroup analyses by age categories, gender, race, and study sites using the intent-to-treat (ITT) population show a similar trend as the primary efficacy analysis in favor of the voretigene neparvovec treatment group.

Table 1. Demographics of the Phase 3 Study (ITT)

Category	Total (n=31)
Age (Years)	
Mean (SD)	15.1 (10.9)
Range (min, Max)	4, 44
Age Groups (Years)	
4-10	14 (45%)
11-17	6 (19%)
>17	11 (36%)
Gender, n %	
Female	18 (58%)
Race, n %	
White	21 (68%)
Asian	5 (16%)
American Indian or Alaska Native	3 (10%)
Black or African American	2 (6%)

Source: FDA statistical review

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

2.1.1The proposed indication

The applicant proposed the following indication: "For the treatment of patients with vision loss due to confirmed biallelic *RPE65* gene mutation-associated retinal dystrophy"; "for patients who have sufficient viable retinal cells as estimated by optical coherence tomography (OCT) as an area of retina within the posterior pole of >100 micron thickness".

The proposed indication defined the treatment population with the following elements, which will be discussed in Sections 2.1.2 and 2.1.3:

- Clinical feature: Vision loss and retinal dystrophy
- Molecular feature: Confirmed biallelic *RPE65* gene mutation

- Ophthalmology test to select potential responders: Sufficient viable retinal cells estimated by OCT

However, following review of the submission, the indication was modified to: "For the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy." (Section 11.5)

2.1.2 Retinal dystrophy due to RPE65 mutations

Hereditary retinal dystrophies are a broad group of retinal disorders that are manifested by 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).

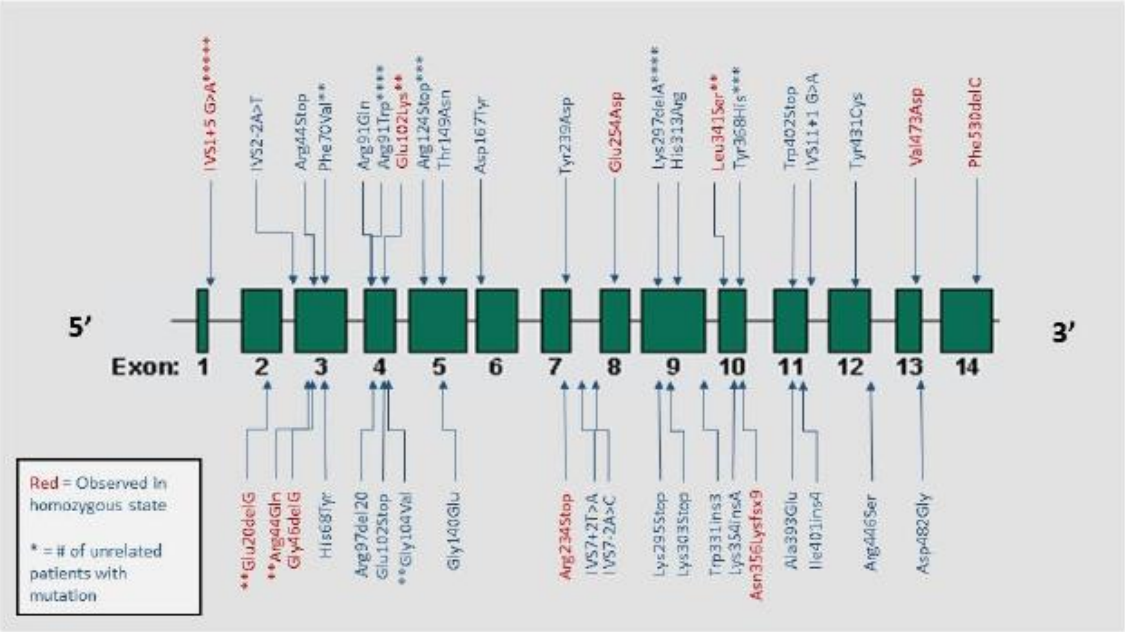
Retinal dystrophy due to *RPE65* mutations includes a heterogeneous group of serious and sight-threatening genetic retinal diseases with various clinical presentations. The majority of the disease population, such as Leber congenital amaurosis (LCA), manifests in early life with severe vision impairment; whereas a small portion of the disease population, such as retinitis pigmentosa, undergo a gradual course of night blindness and visual field loss (see Appendices 13.1, Summary of Applicant's Natural History Study).

Reviewer's comment: As retinal dystrophy due to RPE65 mutations represents various clinical diagnoses/phenotypes, the molecular diagnoses should be used in the indication statement instead of the clinical diagnosis, such as LCA.

2.1.3 Molecular diagnoses

Confirmation of mutation(s) in the *RPE6*5 gene was required for inclusion in the Phase 1 and Phase 3 trials. Both compound heterozygotes and homozygotes were included. Majority of the subjects, 83% (34 of 41), received a genetic diagnosis before enrolling in the trials. All subjects had their genetic diagnosis confirmed at enrollment. Among the 41 subjects that included four pairs of siblings, there were 34 unique mutations in *RPE65* gene (Figure 1).

Figure 1. Location of the 34 Unique Mutations in *RPE65* Gene in Phase 1 and Phase 3 subjects



Source: Figure 19, Page 48, Spark Therapeutics AC Briefing Document for BLA 125610

Reviewer's Comment: There were 34 unique mutations in the RPE65 gene in 41 subjects from the Phase 1 and Phase 3 trials. There were 56 unique RPE65 mutations in 70 subjects in the Natural History Study (see Appendices 13.1). To ensure safe and effective use of voretigene neparvovec for patients with retinal dystrophy due to RPE65 mutations, accurate molecular diagnoses are critical. The CMC and clinical teams discussed the need for an in vitro companion diagnostic device. As the molecular diagnoses are done by Clinical Laboratory Improvement Amendments (CLIA)-certified labs routinely within medical practice, and the efficacy and safety of voretigene neparvovec were derived from subjects whose diagnoses were made by the CLIA-certified molecular diagnosis laboratories (See Appendices 13.2), a companion diagnostic is not needed.

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

There is no approved pharmacological treatment for patients with biallelic *RPE65* mutation-associated retinal dystrophy.

There is a FDA-approved device indicated for severe retinitis pigmentosa. The Argus II Retinal Prosthesis System, manufactured by Second Sight Medical Products, is indicated to provide electrical stimulation of the retina to induce visual perception in blind adult patients with severe to profound retinitis pigmentosa.

2.3 Safety and Efficacy of Pharmacologically Related Products

This section summarizes preliminary safety, bioactivity, and preliminary efficacy data generated from early-phase studies of similar investigational gene therapy products for the identical indication. The mechanism of action of these investigational products is very similar. Table 2 summarizes two independent trials from two research groups.

As shown in Table 2, subretinal injection of the investigational products showed improvement in retinal light sensitivity testing as well as mobility testing in both studies. The effects sustained over three years but declined gradually over time as reported by Jacobson et al *(Reference 49, 51, and 53);* and declined after one year as reported by Bainbridge et al *(Reference 46 and 55).*

Reviewer's Comment: The results of these two publications are similar to the results of FST and mobility testing noted for voretigene neparvovec although the effect did not sustain beyond 1-3 years in the two studies. The reason is not clear. It may be due to the difference between voretigene neparvovec and the two investigational products developed by other investigators. The efficacy of voretigene neparvovec has been sustained for at least two years (Phase 3) and for over three years (Phase 1) (Figure 3).

Table 2. Subretinal Injection of Similar Investigational Products for Similar Indication

Publication	**Bainbridge et al. NEJM 2015**	**Jacobson et al. Arch Ophthalmology 2012;and Jacobson et al. NEJM 2015**
Product	AAV2/2 carrying RPE65 gene	AAV2 carrying hRPE65 gene
Indication	LCA due to mutation in RPE65	LCA due to mutation in RPE65
Design	Phase 1/2, open-label, two-dose, worse eye	Phase 1, open-label, 4 doses, two injection methods, worse eye
# of Subject	Total=12 (6-23 years); low dose: ($1x10^{11}$) n=4; high dose: $10X10^{12}$, N=8	Total=15 (11-30 Years); 5 dose cohorts
Study duration	3 years	3 -5 years
Endpoints	VA, contrast sensitivity, color vision, spectral sensitivity, VF, vision-guided ambulatory navigation	dark-adapted full-field sensitivity testing, VA, immune response, VF, pupillometry, mobility, OCT, immune response
Efficacy	Improvement in retinal sensitivity of various levels (n=6), peaking at 6-12 months, then declined;	Improvement in light sensitivity in the treated eyes, the effect was declined after three years; improved mobility as a group
Safety	Intraocular inflammation (n=3); worsening VA (n=2)	Procedure-related adverse events
Preclinical finding	Dose-response in dog studies	

Source: reference 46, 49, 51, 53, and 55

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

2.4.1 Foreign experience (Regulation)

The product is not approved in any country. No foreign clinical data were submitted in the BLA.

2.4.2 Applicant's INDs with various AAV viral vectors

The applicant has other INDs with AAV vector-based gene therapy investigational products for other indications. The major safety issue has been liver toxicity with elevated aminotransferases, in which the investigational product was delivered intravenously. The immune reaction caused asymptomatic elevation of aminotransferases as well as decreased expression of the transgene. The immune reaction was found to be T-cell mediated and was managed by systemic corticosteroids (Reference #28).

2.4.3 Approved gene therapy with AAV vector

Voretigene neparvovec is an adeno-associated virus (AAV) vector-based gene therapy. No AAV vector-based gene therapy is approved in the United States.

2.4.4 Adeno-associated viral vector-based investigational gene therapies

AAV vectors have been widely used in clinical trials for a variety of diseases. After searching www.clinicaltrial.gov using "AAV vector" as the search word during this review, this reviewer identified 92 studies using AAV vector-based gene therapy products for the treatment of various genetic diseases, including 26 studies for genetic ocular diseases.

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

Table 3 summarizes the main interactions between FDA and applicant from pre-IND planning stage in 2005 to BLA submission in 2017.

Table 3. Regulatory Milestones

Event#	Date	Milestones
		IND
1	9/20/2005	Pre-IND meeting
2	6/14/2007	IND 13408 submission by sponsor of Children's Hospital of Philadelphia
3	6/24/2008	Orphan drug designation of AAV2-hRPR65v2 for treatment of Leber congenital amaurosis due to RPE65 mutation (LCA2) (#08-2593)
4	12/18/2008	End of Phase 1 type B meeting to discuss a Phase 3 design
5	1/13/2010	Special Protocol assessment (SPA) Request; sponsor later withdrew request
6	9/8/2010	Type C meeting to discuss mobility test as primary efficacy endpoint
7	5/10/2011 & 10/2/2014	Type C meeting to discuss CMC issues in support of Phase 3 trial
8	6/29/2011	FDA Cellular, Tissue, and Gene Therapies Advisory Committee meeting: Cellular and Gene Therapies for Retinal Disorders (general discussion, not on specific products)
9	4/24/2012	Clinical hold due to SAE of endophthalmitis
10	1/13/2014	Transfer of IND 13408 from the Center for Cellular and Molecular Therapeutics, Children's Hospital of Philadelphia (CHOP) to Spark Therapeutics
11	9/24/2014	Sponsor received Breakthrough Therapy Designation for treatment of nyctalopia (night blindness) in patients with Leber congenital amaurosis due to RPE65 mutation
		Pre-BLA
12	1/15/2015	Type C meeting to discuss the adequacy of nonclinical data in support of a BLA submission
13	6/16/2015	Type C meeting to discuss the indication, diagnosis, primary endpoint analysis, and clinical data submission in preparation for a BLA submission
14	7/21/2015	Advice on Statistical Analysis Plan of Phase 3 protocol
15	3/18/2015	Orphan Drug designation granted for treatment of retinitis pigmentosa due to autosomal recessive RPE65 gene mutations
16	3/25/2016	Pre-BLA meeting to discuss a rolling BLA submission and priority review status
17	11/29/2016	Orphan-Drug designation granted for the use of "adeno-associated viral vector type 2 expressing human recombinant retinal pigment epithelial 65KDa protein gene for the treatment of inherited retinal dystrophy due to biallelic *RPE65* mutations."
		BLA Submission
18	4/26/2016	BLA rolling submission part 1: Nonclinical information
19	2/21/2017	BLA rolling submission part 2: Clinical information
20	5/16/2017	BLA rolling submission part 3: CMC information
21	7/14/2017	Accepted for filing; Priority review; Pediatric Rare Disease Designation
22	10/12/2017	Advisory Committee Meeting to discuss safety and efficacy of BLA 125610
23	1/12/2018	PDUFA Goal Date

Source: Module 1.6.3; IND 13408 amendments; Clinical reviews

The main regulatory events during product development are discussed below:

AC meeting June 2011

FDA held the CTGTAC meeting for Cellular and Gene Therapies for Retinal Disorders on June 29, 2011 to address issues important to the development of cellular and gene therapies for retinal disorders, including Leber Congenital Amaurosis and retinitis pigmentosa. The issues discussed included efficacy endpoints, contralateral eye or repeat

eye administration, surgical concerns of product delivery, immunological concerns related to cellular and gene therapy products, and preclinical assessment (see detail in Section 5.4.1).

The development of the primary efficacy endpoint

Table 4 chronicles the important interactions with the applicant in the development of the primary endpoint, the multi-luminance mobility testing **(**MLMT).

Table 4. Development of the Primary Endpoint: Multi-Luminance Mobility Testing (MLMT)

Time Line	Primary Efficacy Endpoint Discussion
2008 (EOP1)	Exploratory efficacy endpoints included VA, VF, FST, pupillary response, mobility test
2009 (Amendment 18, SPA)	FDA disagreed with the proposed efficacy endpoint of improvement in pupillary light reflex. Sponsor withdrew SPA.
2010 (Amendment 25, Type C)	Sponsor sought advice on using mobility test as a primary efficacy endpoint; the FDA made recommendations with CDER and CDRH input.
2012 (Amendment 34)	Sponsor revised the Phase 3 protocol and mobility test; FDA recommended further revision and AI (Additional Information) letter was sent.
2013 SAP	Sponsor revised the efficacy endpoint based on FDA AI letter: Summation of MLMT score: right eye + left eye + both eyes
2014 SAP	Sponsor revised the primary endpoint to performance of MLMT using both eyes, based on EMA's input. FDA recommended co-primary endpoints, including MLMT score change using both eyes and using the first-treated eye.
June 15, 2015 (Amendment 64, Type C)	FDA recommended co-primary endpoints of MLMT score change using both eyes and using the first-treated eye
July 21, 2015 (Amendment 65, Final SAP)	FDA disagreed with applicant's plan of MLMT score change using both eyes as the sole primary endpoint and recommended co-primary endpoints of MLMT score change using both eyes and using the first treated-eye; FDA recommended analyzing each eye separately for FSA and VA instead of using the average values; FDA recommended using ITT for primary analysis instead of using mITT.

Source: Module 1.6.3; IND 13408 amendments; Clinical reviews for IND 13408

Type B meeting to discuss the Phase 3 study design, June 16, 2015

FDA agreed that the change in the MLMT using both eyes could serve as one of the primary efficacy endpoints. However, as FDA was concerned that the MLMT score using both eyes would represent the better seeing eye, FDA recommended a co-primary efficacy endpoint that compared the score changes in the MLMT using both treated eyes and the first-treated eye to the respective eyes in the control group. FDA emphasized that the success for efficacy would be declared if both primary endpoints were statistically significant.

Designation of Orphan Drug, Breakthrough Therapy/Priority Review, and Rare Pediatric Disease Status

- Orphan Drug designations were granted for LCA2 in 2008, RP in 2015, and retinal dystrophy due to *RPE65* mutations in 2016 (Table 3, event #3, 15, and 17)
- Breakthrough Therapy Designation was granted in 2014 (Table 3, event #11).
- The Rare Pediatric Disease Designation was granted in 2017 (Table 3, event #21)

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The BLA submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. This BLA was filed on July 15, 2017 without any filing issues from all review disciplines.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The review focused on compliance with good clinical practices (GCP), including informed consent, site-specific issues, and whether the clinical trials were conducted in accordance with acceptable ethical standards. Based on review of Section 5 of the clinical study report for Phase 1 (Studies 101 & 102) and Phase 3 studies, the clinical studies were conducted in accordance with Good Clinical Practice, CFR regulations, and IRB rules.

Bioresearch Monitoring (BIMO) inspections were conducted at two clinical sites that participated in the conduct of the Phase 3 study. The inspections did not reveal any issues that impact the data submitted in this application (FDA BIMO Letters).

3.3 Financial Disclosures

Table 5 lists the principal investigators (PI) for the three study sites for the Phase 1 and Phase 3 studies.

Table 5. List of the Principal Investigators in Three Study Sites

Study Site (site#)	Principle Investigators	Phase
CHOP (#001)	Albert M. Maguire, M.D.	Phase 1 (Studies 101 and 102) & Phase 3
IA (#005)	Stephen R. Russell, M.D.	Phase 3
Italy (#002)	Francesca Simonelli, M.D.	Phase 1 (Study 101)

Note: CHOP: Children's Hospital of Philadelphia; IA: University of Iowa; Italy: Second University of Naples. Source: Module 5.3.5.1 & 5.3.5.2; List of Investigators and Qualifications

There were a total of 35 investigators and sub-investigators involved in the Phase 1 and Phase 3 studies at three study sites (Children's Hospital of Philadelphia, University of Iowa, and Second University of Naples, Italy). Four of the 35 investigators have financial interests and arrangements with the applicant.

Table 6 summarizes the four investigators who had financial interests and arrangements with the applicant. Of particular concern are the financial disclosures from Drs. Bennett and Maguire, who own the patents for this product.

Table 6. Summary of Four Investigators with Disclosed Interest/Arrangement

Name & Title	Covered Trials	Type of Financial Interest/Arrangement	Minimization of potential Bias
Jean Bennett, M.D., Ph.D.	Phase 1 & 3	• Funded by applicant for (b) (4), (b) (6) for a trial as director and investigator (spouse) • (b) (4), (b) (6) for bona fide scientific consulting services • Co-inventor with spouse, on patents related to voretigene neparvovec	• Fund to University • Some consult not related to the product • Waived any financial interest in patents
Daniel C. Chung, DO	Phase 1 & 3	• Became a full-time employee of the applicant in December 2014 and he discontinued serving as clinical investigator. He is paid with an annual salary and equity interest in company stocks.	• Discontinued as investigator
Albert M. Maguire, M.D.	Phase 1 & 3	• Funded by applicant for (b) (4), (b) (6) for a trial as co-director (spouse) and investigator • (b) (4), (b) (6) for bona fide scientific consulting services for spouse, Dr. Bennet • Co-inventors with spouse, on patents related to voretigene neparvovec	• Fund to University • Some consult not related to the product • Waived any financial interest in patents
Stephen R. Russell, M.D.	Phase 3	• Compensated (b) (4), (b) (6) for speaking on behalf of the applicant presenting Phase 3 data in July 2016	• Payment was below FDA threshold of $25,000.

Source: Module 1.3.4

To evaluate the potential impact of this proprietary interest of the principal investigators involved in study site 001 (CHOP), the reviewer and the statistician did a subgroup analysis on the primary efficacy outcome in both study sites, CHOP and IA, in the Phase 3 study. As shown in Table 7, the performance of MLMT at CHOP study site is not superior to that in IA site. Therefore, the reviewer concluded that bias resulting from the financial interest does not impact the interpretability of the efficacy outcome of the Phase 3 trial. Further, to minimize the potential bias, both Dr. Bennet and Dr. Maguire have waived any financial interest in the patents related to the product.

Table 7. Subgroup Analysis of Multi-Luminance Mobility Test Score Change by Study Sites

	Treatment (n=21)	**Control (n=10)**
CHOP		
N	11	8
Mean (SD)	1.6 (1.2)	0.3 (1.2)
Range (min, max)	0, 3	-1, 2
Quartiles (Q1, Median,	1, 1, 3	-1, 0.5, 1
IA		
N	10	2
Mean (SD)	1.9 (1.0)	0 (0)
Range (min, max)	1, 4	0, 0
Quartiles (Q1, Median,	1, 2, 2	0, 0, 0

Source: FDA Statistical Review

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

CBER conducted a pre-license inspection (PLI) of Spark Therapeutics Inc., Philadelphia PA, from August 21 - 25, 2017 for voretigene neparvovec drug substance manufacturing. At the conclusion of this inspection, a Form FDA 483 was issued. The firm responded to the observations and the corrective actions were found to be adequate. This inspection was classified as voluntary action indicated (VAI).

The applicant and the FDA reached agreements on the following CMC Postmarketing Commitments regarding

- the shipping validation study protocol
- (b) (4) and tests for particulate matter for the Drug Product and Diluent
- an analysis of the lot release test results obtained from all Drug Substance (DS) and Drug Product (DP) lots manufactured within the first (b) (4)
- stability studies on the HEK293 Master Cell Bank (MCB) used for drug substance manufacture
- qualification of the (b) (4) .

4.2 Assay Validation

The following assays were validated by the applicant:

- Enzyme-Linked Immunosorbent Assay (ELISA) for the Detection of Anti-AAV2-Capsid Antibody in Human Serum
- ELISPOT Method for the Detection of Human PBMC Interferon-gamma Responses to AAV2 Capsid

- ELISpot Method for the Detection of Human PBMC Interferon-gamma Responses to RPE65
- AAV2-hRPE65v2 Gene Therapy Vector Quantitation Assay Validation

Reviewer's Comment: per the CMC reviewer, the assays were well-controlled, sensitive, and accurate.

4.3 Nonclinical Pharmacology/Toxicology

There were no unresolved issues with the preclinical review team. Relevant preclinical information with its significance is summarized as following:

Both *in vitro* and *in vivo* preclinical studies provided the basis for the clinical trials, such as dose-response expression of RPE65 protein and improvement of visual function and behavior in mice and dogs.

Ocular histopathology showed a mild immune response due to re-administration of AAV2-hRPE65v2 sequentially to the same eye of the RPE65 mutant dogs.

No evidence of cellular immune reactions to AAV2 capsid and RPE65 protein were identified in non-human primates (NHPs). Transient humoral immune reactions were found in isolated cases in dogs and NHPs.

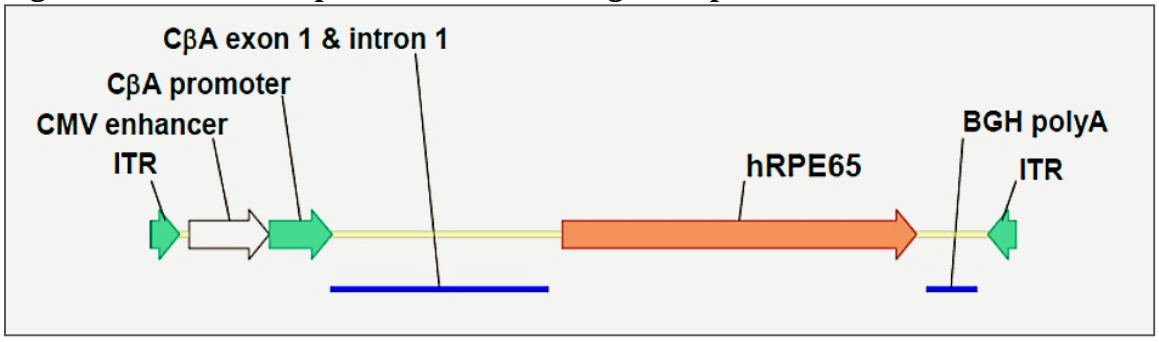
Animal studies to evaluate safety pharmacology, developmental and reproductive toxicity, genotoxicity, and carcinogenicity/tumorigenicity were not conducted for AAV2-hRPE65v2.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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*) (Figure 2).

Figure 2. Schematic representation of voretigene neparvovec



Source: Applicant's BLA

RPE65, an isomerase, is one of the enzymes in the visual cycle catalysing the conversion of all-trans-retinyl ester to 11-cis-retinal for the biological conversion of a photon of light into an electrical signal within the retina. Mutations in *hRPE65* lead to loss of visual function and retinal dystrophy. Voretigene neparvovec is administered via subretinal injection to a small portion of the posterior retina. Voretigene neparvovec is expected to improve vision by delivering a normal copy of hRPE65 to a portion of retinal pigment epithelium cells in patients with biallelic *RPE65* mutations-associated retinal dystrophy.

4.4.2 Human Pharmacodynamics (PD)

Injection of voretigene neparvovec into the subretinal space results in transduction of retinal pigment epithelial cells with a cDNA encoding normal human RPE65 protein, providing the potential to restore the visual cycle.

4.4.3 Human Pharmacokinetics (PK)

Biodistribution (within the body) and Vector Shedding (excretion/secretion)

Voretigene neparvovec vector DNA levels in various tissues and secretions were determined using a quantitative polymerase chain reaction (qPCR) assay.

Vector shedding and biodistribution were investigated in a study measuring vector DNA in tears from both eyes, and from serum, and whole blood of subjects in the Phase 3 clinical study as shown in Table 8**.**

Table 8. Summary of Phase 3 Vector Shedding and Biodistribution Data

Category	Total N = 29
Subjects with Any Positive Samples	14 (48%)
Subjects with Only Positive Tear Samples	11 (38%)
Subjects with Only Positive Serum Samples	1 (3%)
Subjects with Both Positive Tear and Serum Samples	2 (7%)

Note: No whole blood samples were positive for AAV2-hRPE65v2 vector DNA.
Source: Module 2.5.5.5.2: Clinical Overview. Study 301 CSR and Study 301 CSR Addendum 2016

In the 29 subjects who received bilateral administration of voretigene neparvovec, vector DNA was present in tear samples of 13 subjects (45%). Peak levels of vector DNA were detected in the tear samples on Day 1 post-injection, after which no vector DNA was detected in a majority of the subjects (8 of 13). Three subjects (10%) had vector DNA in tear samples until Day 3 post-injection, and two subjects (7%) had vector DNA in tear samples for around two weeks post-injection. In another two subjects (7%), vector DNA was detected in tear samples from the uninjected (or previously injected) eye until Day 3 post-injection. Vector DNA was detected in serum in 3/29 (10%) subjects, including two with vector DNA in tear samples up to Day 3 following each injection. In summary, vector was shed transiently and at low levels in tears from the injected eye in 45% of the subjects in the Phase 3 trial, and occasionally (7%) from the uninjected eye until Day 3 post-injection.

Specific Populations
No pharmacokinetic studies have been conducted.

Drug Interaction Studies
No interaction studies have been performed.

4.5 Statistical

The statistical team confirmed the primary endpoint analysis and secondary analysis, and conducted exploratory analysis for the visual acuity.

The statistical team provided sensitivity analyses regrading subcomponent of the MLMT, the accuracy score and time score, to determine whether the outcomes of these subcomponents were consistent with overall MLMT score change. The statistical team concluded that the efficacy of voretigene neparvovec was supported by the Phase 3 trial results.

4.6 Pharmacovigilance

The applicant proposed the following postmarketing risk mitigation plan:

1. Pharmacy and surgical training programs
2. Postmarketing safety registry
3. Ongoing LTFU of 15 years for long-term safety and efficacy from the Phase 1 and 3 trials conducted under IND 13408

4.6.1 Postmarketing registry study

The applicant proposed a multicenter, multinational, observational postmarketing authorization safety registry, following subjects for five years after subretinal administration. The goal of the study is to collect adverse events, including development or exacerbation of oncologic, hematologic, neurologic, and auto-immune diseases; adverse events due to the administration procedure, including eye inflammation and infection, increased intraocular pressure, retinal tear, retinal disorder, macular hole, maculopathy, and cataract progression or formation, and pregnancy outcomes. The registry is expected to collect the following information: demographics, dosing and administration information, serious adverse events and adverse events of interest, the safety information possibly attributable to voretigene neparvovec. The source of information is expected to come from annual contact with health care providers to solicit reportable AEs or occurrence of pregnancy and pregnancy outcomes.

The following recommendations were sent by the pharmacovigilance reviewer and were accepted by the applicant:

FDA's recommendations: "For the postmarketing patient safety registry, please consider requiring at least 40 patients be enrolled and at least a 5-year period of enrollment. Having the study continue enrollment until both criteria are met would ensure the study includes a minimum number of patients. Also, consider requiring that the patients in the registry be examined by an ophthalmologist at least once per year."

Applicant's response: "We did not have a minimum or maximum number stated, but we will incorporate this recommendation to require at least 40 patients be enrolled. We are planning on enrolling for 5 years. We agree it is reasonable to require an ophthalmology exam at least once a year.

Reviewer's Comment: although the purpose of the registry is to collect safety information, FDA recommends that the applicant collect data on long-term efficacy, such as MLMT, VA, and VF. However, the applicant did not consider it necessary because it may not provide any additional information beyond what will be collected in the ongoing long-term-follow-up plan of 15 years under IND 13408. In addition, the collection of efficacy data from multiple treatment sites will introduce even more variability into these measures, and it is not feasible to perform some tests, such as MLMT and FST at many of the treatment sites.

4.6.2 FDA's decision on postmarketing surveillance

Based on review of available data, and input from CDER and the CTGTAC meeting, the pharmacovigilance and clinical review team concludes that the safety concerns from the Phase 1 and Phase 3 studies can be mitigated through routine medical management, appropriate labeling, as well as the voluntary postmarketing plans proposed by the applicant. The reviewed safety data do not warrant a Risk Evaluation and Mitigation Strategies (REMS), a safety postmarketing requirement (PMR) study, or a safety postmarketing commitment (PMC) study.

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

The sources for the review include (1) the licensing application, and (2) sources external to the BLA, such as data from IND 13408 that support this BLA submission and the related publications submitted by the applicant and other researchers.

5.1 Review Strategy

A thorough accounting of all the BLA/IND documents considered in the review is documented in Section 5.2.

With respect to the evaluation of efficacy, this reviewer focused on the data from Study 301, the single Phase 3 trial, by exploring various analytical approaches such as mean and median values for the endpoints, and the responder rates to evaluate the robustness of the efficacy outcomes. As the trial sample size was small, individual subject level data was also evaluated. The preliminary evidence of efficacy obtained from Phase 1 study was reviewed as supportive information. The evaluation of safety was based on pooled data from both Phase 1 and Phase 3 studies as the study populations were similar.

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

Table 9 consists of a comprehensive list of all the materials from the BLA that were considered for the review. The eCTD module number and location are listed next to the review material.

Table 9. Summary of the Review Material for BLA 125610

Review Material	Module
Financial disclosure forms (n=4)	1.3.4
Draft labeling for PI, carton, container	1.14
Post-marketing pharmacovigilance plan (protocol for a safety registry of 5 years)	1.16
Clinical Overview	2.5
Integrated summary of safety (n=41)	2.7.3
Integrated summary of efficacy (n=31)	2.7.4
Phase 3 (301) study report (n=29); video for mobility test	5.3.5.1
Phase 1 (101) study report (n=12), treating the first eye	5.3.5.2
Phase 1 (102) study report (n=11), treating the second eye	5.3.5.2
Mobility test validation study (n=60)	5.3.5.4
Natural history study (n=70)	5.3.5.4

Source: BLA 5.3 Table of Studies/Clinical Trials

5.3 Table of Studies/Clinical Trials

Table 10 summarizes basic information and key aspects of the designs and outcomes of all the clinical studies in the BLA submission, including the Phase 1 study (two protocols: Study 101 and Study102), the Phase 3 study (two parts: 301 and 302).

Table 10. Summary of Phase 1 and Phase 3 Clinical Trials under IND13408

Trial	Protocols/parts	Study Period	Study Design	Sample Size
Phase 1	• Study 101 (AAV2-RPE65v2-101) • Study 102 (AAV2-RPE65v2-102)	2007-2014 2010-2014	• Study 101: Phase 1, dose-escalation (three dose cohorts), treating the first eyes • Study 102: treating the second eyes with high-dose	n=12 n=11
Phase 3	• Study 301 (AAV2-RPE65v2-301) • Study 302	2012-2015	Phase 3, open-label, randomized, controlled, cross-over; • Study 301: main study • Study 302: cross-over	n=31 • Treatment group, n=21 • Control/Cross-over group, n=10
Total				Enrolled n=43 Treated n=41

Source: adapted from Module 5.2 Tabular List of All Clinical Studies

5.4 Consultations

5.4.1 Advisory Committee Meetings

a. FDA Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) Meeting on Retina Disorders *(Reference 21 and 22)*

The CTGTAC meeting was held in Silver Spring, Maryland on June 29, 2011 to discuss cellular and gene therapy products for the treatment of retinal disorders. Guest speakers, including the investigators of IND 13408 that supports this BLA, provided information related to (1) animal models of retinal disease, and (2) the evaluation of safety and efficacy endpoints, including clinical experience, with gene therapy products for the treatment of Leber Congenital Amaurosis and neovascular age-related macular degeneration.

This AC meeting discussed multiple important issues, including potential immune response, surgical procedures, and selection of efficacy endpoints for retinal diseases, which guided the development of voretigene neparvovec.

b. FDA Cellular, Tissue, and Gene Therapies Advisory Committee on BLA 125610 *(Reference 23 and 24)*

The CTGTAC meeting was held on October 12, 2017 to provide feedback to FDA regarding efficacy and safety, and an overall benefit-risk assessment of voretigene neparvovec. The AC members discussed the three questions raised by the FDA, briefly, (1) the clinical meaningfulness of 2-light level improvement in MLMT (i.e., an MLMT score change of 2); (2) the optimal disease stage to treat patients taking into account: clinical stage, extrapolation to early disease, the minimal age to treat, potential safety concerns of subretinal injection and systemic corticosteroid use in children; and (3) consideration for repeat administration of voretigene neparvovec.

Overall, the AC members considered that an MLMT score change of 2 is clinically meaningful although the design of the MLMT is not perfect as there is an uneven distribution between the light levels. Additional inputs/considerations from AC members include:

- results of other outcomes, such as FST support the results of the MLMT; the live testimonies from five trial participants and their parents noted meaningful improvement in the quality of life following administration of voretigene neparvovec;
- the potential risks associated with subretinal injection of voretigene neparvovec and concomitant corticosteroid use are acceptable for pediatric population, even in the very young subjects;
- retinal cellular proliferation is not complete until 8 to 12 months of age, and voretigene neparvovec would potentially be diluted or lost during the cellular proliferation process if patients are treated before 12 months of age;
- further study(ies) are needed to support repeat administration of voretigene neparvovec to individual eyes.

- All 16 AC members voted "Yes" to support an overall favorable benefit-risk profile for voretigene neparvovec.

Reviewer's Comment: Based on AC members' inputs, clinical team expanded the indicated patient population to one year of age and older in the PI. In addition, based on AC members' input on the potential risks of voretigene neparvovec and FDA's own review of safety data, FDA determined that there is no need for a REMS, a safety PMR study, or a safety PMC study.

5.4.2 External Consults/Collaborations

From the submission of the original IND 13408 in 2007 to the submission of this BLA, valuable input has been obtained from the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiologic Health (CDRH) regarding the study design and the development of the novel endpoint, Multi-Luminance Mobility Testing (MLMT). The consultations from CDER and CDRH for the IND and BLA review provided much needed expertise in clinical practice of ophthalmology, in the field of low vision and functional vision, in the design of the clinical trials to support this BLA, and in the maintenance of the inter-center regulatory consistency.

Bernard P. Lepri, OD, MS, Med, from the Division of Ophthalmic, Ear, Nose & Throat Devices, CDRH, provided consultation during the development of MLMT, and participated in the review of the BLA, in particular, the review of the MLMT validation study and Phase 3 study MLMT results.

Wiley A. Chambers, M.D., from the Division of Transplant and Ophthalmology Products, CDER, was involved in each step review of the clinical program, including Phase 1 and Phase 3 study design, efficacy endpoint selection, and development of MLMT. Dr. Chambers' contributions are as follows:

- Attended most internal and sponsor meetings related to IND 13408 and this BLA.
- Participated in the review of the BLA, including the efficacy outcome analysis, MLMT video review, postmarketing plan, and labeling revision,
- Participated in preparation of the AC briefing document and AC meeting discussion.

5.5 Literature Reviewed

During the review of this BLA, this reviewer consulted FDA regulatory guidance documents, and academic literature for background and context regarding the targeted disease and mechanism of action of the product. A list of the literature is provided in Section 12, References.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

The clinical studies that support the BLA include a Phase 1 study with two clinical protocols (Study 101 and Study 102) and a Phase 3 study with two parts (Study 301 and Study 302). The Phase 3 study provides the primary evidence of effectiveness for voretigene neparvovec. Both Phase 1 and Phase 3 studies contribute to the safety

database. This section describes the design and the conduct of the Phase 1 and Phase 3 studies.

6.1 Trial #1 (Phase 1, Study 101 and Study 102)

The Trial #1 is a Phase 1 study including two clinical protocols, Study 101 and Study 102.

6.1.1 Objectives

Study 101

- Primary objective was to determine the safety and tolerability of three different doses administered via subretinal administration to one eye (first-treated eye) of subjects with Leber congenital amaurosis due to *RPE65* mutations.
- Secondary objective was to assess the clinical measures of efficacy in human subjects.

Study 102

- Primary objective was to assess the safety and tolerability of treatment to contralateral eye (second-treated eye) of subjects in Study 101.
- Secondary objective was to evaluate the efficacy of contralateral eye using pre-injection measurement as control.

6.1.2 Design Overview

Study 101

Study 101 was an open-label, dose-exploration safety study. Twelve subjects, who were eight years of age or older at the time of administration, were to receive unilateral subretinal injection (first-treated eyes, chosen with worse function). Three doses were tested sequentially, 1.5×10^{10}, 4.8×10^{10}, and 1.5×10^{11} vector genomes (vg).

Study 102

Study 102 was a follow-on study to Study 101. Eleven of the 12 treated subjects in Study 101 were to receive a subretinal injection in the contralateral eye (second-treated eyes) with only one dose at 1.5×10^{11} vg in a total volume of 300 μL. For observing and mitigating potential immune responses due to the previous treatment in one eye, two parts of the study were planned. In Part 1 of Study 102, three subjects were to be treated with an interval of at least 8 weeks; in Part 2, nine subjects were to be treated after DSMB reviewed the Part 1 safety data and recommended that the study proceed.

One of the 12 subjects in Study 101 was not treated in the second eye due to failing to meet the eligibility criteria as he had glaucomatous changes in the eye to be treated, 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 an extended long-term follow-up (LTFU) planned for a total of 15 years (annual visits for five years plus annual phone or visits for ten years).

6.1.3 Population

Up to 12 adults and children eight years of age and older met the eligibility criteria.

Key enrollment criteria were as follows:

Study 101
Inclusion Criteria

- Eight years of age or older at time of administration
- Diagnosis of LCA
- Molecular diagnosis confirmed due to *RPE65* mutations (homozygotes or compound heterozygotes) by a CLIA (Clinical Laboratory Improvement Amendments)-approved laboratory
- Visual acuity no better than 20/160 or visual field less than 20 degrees in the eye to be injected

Exclusion Criteria

- Insufficient viable retinal cells, as determined by optical coherence tomography (OCT) and/or ophthalmoscopy, 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

Study 102
Inclusion Criteria

- Participants of Study 101
- Visual acuity no worse than light perception
- Sufficient viable retinal cells as determined by OCT and/or ophthalmoscope

Exclusion Criteria

- Preexisting eye condition, such as glaucoma, or complicating systemic diseases

6.1.4 Study Treatments or Agents Mandated by the Protocol

Dose and Regimen
The dose of voretigene neparvovec was defined based on both the vector genome (vg) and the subretinal injection volume (microliter, µL). Three dose-levels were sequentially tested for the first-eye injection in Study 101 (Table 11). 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 (1.5×10^{11} vg / 300 µL), which was concluded to be safe in Study 101. To avoid exposing multiple subjects to unreasonable risks, subjects were staggered for an interval of at least 6 weeks because it took up to six weeks for transgene expression to reach its peak.

Table 11. Dose Cohorts for Study 101 and Study 102

Cohort	Number of Subjects (n)	Dose/Volume
Study 101	12	3 doses
1	3	1.5×10^{10} vg /150µL (low)
2	6	4.8×10^{10} vg /150µL (middle)
3	3	1.5×10^{11} vg /300 µL (high)
Study 102	11	1 dose
Part1	3	1.5×10^{11} vg /300 µL
Part 2	8	1.5×10^{11} vg /300 µL
Total	12	

Source: Adapted from Study Report of 101 and 102

Formulation

Voretigene neparvovec is supplied in 1 mL aliquots in 1.5 mL cryovials as a suspension at a concentration of approximately 5×10^{12} vector genomes per milliliter. The vector product is formulated in sterile water containing 180mM Sodium chloride, 10mM Sodium phosphate, 0.001% Pluronic (b) (4) Poloxamer 188), pH7.3. The Excipient (diluent) is supplied as 4.5 mL aliquots in 5 mL cryovials. It is composed of sterile water containing 180mM Sodium chloride, 10mM Sodium phosphate, 0.001% Pluronic (b) (4), pH 7.3. The drug was stored at temperature of (b) (4) degrees Celsius.

Concomitant Use of Corticosteroid

- Systemic corticosteroid: Prednisone was given orally at 1mg/kg/day (maximum dose of 40 mg/day) starting 3 days prior to injection of each eye and continued for a total of 10 days, followed by 0.5 mg/kg/day for an additional 7 days. The systemic corticosteroid was dispensed to subjects to reduce any potential immune response to AAV2 capsid and transgene product, RPE65.
- Ocular corticosteroid and prophylactic antibiotics:
    - Sub-tenon/retrobulbar infusion of 1 mL triamcinolone (40mg/mL)
    - Subconjunctional injection of 0.5 mL of 4 mg/mL dexamethasone solution
    - Topical ocular dressing with one inch of prednisolone acetate 0.6%, gentamicin sulfate 0.3% or tobramycin 0.3%, dexamethasone 0.1% ointment
    - 0.5 mL of 50 mg/ml vancomycin or cefazolin

Reviewer's Comment: ocular corticosteroids were not used in the Phase 3 trial due to risk of increased intraocular pressure, infection, and cataract formation.

Prohibited Medications

- Investigational agents other than AAV2-hRPE65v2
- High dose (>7500 retinol equivalent units or >3300 IU) per day of vitamin A
- Tretinoin-containing skin cream (e.g., Retin-A)
- Isotretinoin
- Viagra (sildenafil) or related compounds used to treat erectile dysfunction
- Hydroxychloroquine, chloroquine, mellaril, or any related retino-toxic compounds

Route and Mode of Administration

Voretigene neparvovec was administered via subretinal injection. See Appendix 13.3 for detailed injection procedure.

Of note, the surgical procedure was modified somewhat from Phase 1 to Phase 3 based on accumulated experience with product delivery.

6.1.5 Directions for Use (device)

- Injection device included commercially available cannula designed for subretinal injection (Bausch and Lomb Storz® Retinal Cannula (REF E7365) or BD Visitec™ MVR Cannula; REF 585188).
- Comparability tests were done by the applicant to justify the use of some brands of commercially available injection cannula.

6.1.6 Sites and Centers

- Site #001: Children's Hospital of Philadelphia (administration site; overall study conduct)
  PI: Albert M. Maguire, MD (retinal surgeon), Associate Professor, Director of Retina-Vitreal Service, University of Pennsylvania, Scheie Eye Institute

- Site #002: Second University of Naples, Italy (subject referral/follow-up only; no product administration was performed on this site)
  PI: Francesca Simonelli, MD, Associate Professor of Ophthalmology, Second University of Naples, Naples, Italy

6.1.7 Surveillance/Monitoring

This section summarizes the surveillance/monitoring plans for both safety and efficacy.

- Follow-up visits: the schedules for safety and efficacy evaluation were similar for both Study 101 and Study 102, as shown in Table 12 and Table 13.
- Long-term follow-up: five years of annual visits to evaluate safety and efficacy plus ten years of annual phone contact or visit, mainly for clinical questionnaire (see Section 6.2.7, Table 19B)
- Two contract research organizations (CROs) were responsible for study monitoring to ensure integrity of the data. The CROs conducted site visits for overall function evaluation and made recommendations for resolving deficiencies.
  - (b) (4) (Sept 2007 – Dec. 2011)
  - (b) (4) (starting Dec. 2011)
- A Data and Safety Monitoring Board (DSMB) provided oversight and monitoring of the trial conduct to ensure the safety of participants.

Table 12. Schedule of Assessments, Study 101

Time Point/ Procedure	Baseline		Day	Days											Year	
	B1	B2	-3	0	1	2	3	14	30	60	90	180	270	365	1.5	2 to 5
Informed consent	X															
History/PE	X				X				X		X			X		
Pregnancy test (blood test)	X			X												
Screen for HIV/hepatitis B & C	X															
Begin prednisone			X													
Discontinue prednisone								X								
Vital signs	X	X		X	X	X	X	X	X					X		
Hematology	X				X		X	X	X		X			X		
Chemistry	X			X	X		X	X	X		X			X		
PBMC collection	X							X	X		X					
Urinalysis	X			X	X		X	X	X		X			X		
AAV Ab	X							X	X		X			X		
RPE65 Ab	X							X	X		X			X		
Peripheral blood/Tear QPCR	X			X	X	X[1]										
Ophthalmic exam [2]	X	X			X	X	X[3]	X	X	X	X	X	X	X	X	X
OCT	X									X		X		X	X	X
Acuity	X	X			X	X	X	X	X	X	X	X	X	X	X	X
Color vision	X	X							X	X	X	X	X	X	X	X
Contrast sensitivity		X										X		X	X	X
ERG	X									X				X	X	X
Visual field test		X							X	X	X	X	X	X	X	X
Pupillometry		X							X	X	X	X	X	X	X	X
Nystagmography (ocular motility)		X									X	X	X	X	X	X
Fundus photography	X			X					X			X		X	X	X
Quality of life	X									X		X		X	X	X
Mobility testing		X									X	X		X	X	X
Adverse event recording	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X

Subjects may have been seen at more than one study site. If a referring/follow-up site was utilized: B1 and B2 visits occurred at both the referring/follow-up site (SUN) and the administration site (CHOP); Visits Day 0 to Day 3 occurred at CHOP; Visits Day 14 and beyond occurred at the referring/follow-up site until the site was closed in June 2011. Day -3 is not a study visit, rather when eligible subjects began taking systemic corticosteroids.

Source: Clinical Study Report for Study 101, Table 9.3, Page 35

Table 13. Schedule of Assessments, Study 102

Assessment	Baseline	Day					Week								Day		Year
	1&2	-3	0	1	2	3	1*	2	3*	4	5*	6*	7*	8	90	180	1
Informed consent	X																
Physical exam, vital signs	X																X
Pregnancy test (if applicable)	X		X														
HIV screening	X																
Begin prednisone		X															
Discontinue prednisone								X									
Anesthesia consult, vital signs			X														
Vector administration			X														
Discharge exam, vital signs				X													
Hematology/chemistry	X		X												X		X
Urinalysis	X		X												X		X
Peripheral blood & tear PCR^	X			X	X	X	X										
ELISPOT (PBMC)	X						X	X	X	X	X	X	X	X	X		
AAV and *RPE65* antibodies	X						X			X				X		X	X
Ophthalmic exam[†]	X			X	X	X	X[††]	X		X				X	X	X	X
Optical Coherence Tomography	X							X		X				X	X	X	X
Fundus photography	X		X					X		X				X	X	X	X
Visual/retinal function tests	X							X		X				X	X	X	X
AE and ConMed recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*Visits marked with an asterisk are scheduled visits for **Part 1** subjects only.

Day -3 is not a study visit. Subjects will begin taking systemic corticosteroids prescribed during the baseline visits following the informed consent and confirmation of eligibility criteria.

Visual/retinal function tests will consist of the following evaluations: mobility testing; pupillometry; visual acuity tests; visual field tests; full field light sensitivity threshold testing; and contrast sensitivity.

^Blood/tear polymerase chain reaction (PCR) will be continued until two consecutive samples test negative: Tear collection will occur at each study visit until this result is obtained; blood will be tested until this result is obtained from the scheduled blood draws. Based on vector shedding analysis from the initial Phase 1 study (101), it is not anticipated that specimens for vector shedding will be collected beyond Week 1.

[†]All ocular exams will be performed on both eyes.

[††]If ocular inflammation is present at the Day 3 visit, an additional ophthalmic exam will be included at Day 7 regardless of study group.

Source: Clinical Study Report for Study 102, Table 9.2, Page 37

6.1.8 Endpoints and Criteria for Study Success

Safety Assessment
As the evaluation of safety was the main goal of the study, the following were assessed:

Study 101

- Physical examination with vital signs
- Adverse event recording
- Concomitant medications
- Clinical labs: serum chemistries, hematology, serum for AAV and *RPE65*-specific neutralizing antibodies and antigen-specific reactivities, peripheral blood and tear PCR to detect vector spread
- Serial ophthalmic exams (including visual acuity measurement, slit lamp examination, applanation tonometry and gonioscopy as needed in cases of increased intraocular pressure)
- Direct and indirect ophthalmoscopy

Study 102
Same as in Study 101 with focus on the following:

- Immunology studies for AAV antibodies (AAV Ab) and antibodies for retinal pigment epithelium 65 kDa protein (*RPE65* Ab)
- Peripheral blood mononuclear cells (PBMCs) using ELISPOT assay for cell-mediated immune response

Efficacy Assessments

Study 101
As there was limited precedent for testing profound low vision in young subjects, many efficacy endpoints were explored, including the following:

- Visual acuity (ETDRS testing)
- Visual field (Goldmann perimetry)
- Electroretinography (ERG)
- Contrast sensitivity
- Color vision testing
- Pupil function testing
- Mobility testing
- Quality of life assessments (modified for pediatric use from a visual function questionnaire developed by the National Eye Institute)

Study 102
The same as Study 101, with attention to the following assessments:

- Mobility testing
- Pupillary light responses (PLR)
- Full field light sensitivity threshold (FST) testing
- Visual acuity testing
- Visual field testing (Goldmann perimetry)

- Contrast sensitivity

6.1.9 Statistical Considerations & Statistical Analysis Plan

As this was a Phase 1 safety study, no formal hypothesis testing was conducted. Descriptive statistics (number and percentage by dose cohort for categorical data; mean, median, range, standard deviation) were presented for each of the evaluable parameters for change from baseline as well as value at each time point. Missing values were treated as missing without any imputation.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The analyses of efficacy and safety included all subjects who received the product.

6.1.10.1.1 Demographics

Subjects in Study 101 received voretigene neparvovec in their first eye, usually the worst-seeing eye. As shown in Table 14, three eyes were administered the low dose; six eyes were administered the middle dose, and three eyes were administered the high dose. The average age of subjects was 20 years with an age range of 8 to 44 years. Both middle-dose and high-dose cohorts included pediatric subjects.

Table 14. Demographics of Study 101

Category	Low Dose N=3	Middle Dose N=6	High Dose N=3	Total N=12
Age, years				
Mean	23.7	14.7	30.3	20.8
Median (Min, Max)	26 (19, 26)	13.5 (8, 24)	36 (11, 44)	19.5 (8, 44)
Gender, n				
Male	1	4	2	7 (58%)
Female	2	2	1	5 (42%)
Race, n (%)				
White	3	5	3	11 (92%)
Asian	0	1	0	1 (8%)

Source: Adapted from Table 11.1, Clinical Study Report (101), Page 50

Subjects in Study 102 received voretigene neparvovec in their second eye. As shown in Table 15, 11 subjects received the high dose. One subject had apparent worsening of his preexisting glaucoma, an exclusion criterion; therefore, the subject was excluded from Study 102. The average age of the 12 subjects was 22 years, ranging from 11 to 46 years.

Table 15. Demographics of Study 102

Category	High dose, n=11
Age, years	
Mean	22.8
Median (Min, Max)	23 (11, 46)
Gender, n	
Male	6 (55%)
Female	5 (46%)
Race, n (%)	
White	10 (91%)
Asian	1 (9%)

Source: adapted form Table 11.1, Clinical Study Report (102), page 54

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 16 shows the baseline visual acuity and visual field for Phase 1 subjects. The average visual acuity was worse than legal blindness (log of the Minimum Angle of Resolution (LogMAR)≥1.)

Table 16. Baseline Parameters of Subjects in Phase 1

Subject	Age	VA (LogMAR*) (first eye)	VA (LogMAR) (second eye)	VF (degrees) (first eye)	VF (degrees) (second eye)
(b) (6)	26	2.75 (R)	1.75 (L)	41	36
	26	2.75 (R)	1.28 (L)	62	55
	19	1.39 (R)	1.04 (L)	84	136
	17	1.06 (L)	0.75 (R)	1115	1271
	20	1.34 (R)	1.17 (L)	242	467
	9	1.32 (R)	1.18 (L)	463	517
	8	1.03 (L)	0.95 (R)	372	554
	10	1.47 (R)	1.13 (L)	1033	1168
	24	1.01 (R)	0.79 (L)	729	869
	44	3.5 (R)	3.00 (L)	50	99
	36	1.86 (R)	1.6 (L)	233	181
	11	0.96 (R)	0.74 (L)	1218	1294
Total 12	Range 8-44	1.70 (Ave)	1.28 (Ave)	470 (Ave)	554 (Ave)

Note: Low dose cohort: NP-01, 02, 03; Medium dose cohort: (b) (6) ; High dose cohort: (b) (6) .
LogMAR: Logarithm of the minimum angle of resolution (see Section 7.1.5.b)
Source: CSR 101

6.1.10.1.3 Subject Disposition

Table 17 summarizes the subject disposition of Study 101 and Study 102. Subject (b) (6), a 36-year-old subject treated with high dose in Study 101, was not enrolled in Study 102 due to glaucoma changes per examination (preexisting).

Table 17. Subject Disposition for Study 101 and Study 102

	Low Dose, n (1.5×10^{10}vg)	**Middle Dose, n (4.8×10^{10}vg)**	**High Dose, n (1.5×10^{11}vg)**	**Total**
Study 101				
Enrolled	3	6	3	12
Treated	3	6	3	12
Discontinued	0	0	0	0
Study 102				
Enrolled			11	11
Treated			11	11
Discontinued			0	0

Source: Adapted from Clinical Study Report (101), Table 10.1, Page 48; Clinical Study Report (102), Table 10.1, Page 52

6.1.11 Efficacy Analyses for Studies 101 and 102

6.1.11.1 Visual acuity

In the absence of a concurrent control group, visual acuity changes were compared between the treated and the untreated eyes at baseline and at different time points following product administration. The data were standardized to LogMAR scores with lower numbers reflecting better vision. Each 0.1 LogMAR unit represents a five-letter change on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. A change of LogMAR 0.3 is considered clinically meaningful.

Table 18 shows the visual acuity measurement in response to treatment over a follow-up period of five years. Over the five years, 46% of the treated eyes compared to 16% of the untreated eyes had a cumulative improvement of LogMAR 0.3. However, 16% of the treated eyes compared to none of the untreated eyes had a worsening of LogMAR 0.3.

Reviewer's Comment: because of the difficulty to interpret the above findings regarding change in visual acuity (VA) following voretigene neparvovec administration, applicant decided not to use change in VA as the primary endpoint for the Phase 3 trial.

Table 18. Summary of Visual Acuity Changes

Year Post-Treatment	1 n=12	2 n=11	3 n=9	4 n=4	5 n=1	Cumulative n=37
Injected Eye (LogMAR)						
Improved (≥0.3)	7 (58%)	4 (36%)	5 (56%)	1	0	17 (46%)
Stable (±0.2)	3 (25%)	6 (55%)	2 (22%)	2	1	14 (38%)
Worsened (≥0.3)	2 (17%)	1 (9%)	2 (22%)	1	0	6 (16%)
Un-injected Eye LogMAR)						
Improved (≥0.3)	2 (17%)	2 (18%)	1 (11%)	1	0	6 (16%)
Stable (±0.2)	10 (75%)	9 (64%)	8 (56%)	3	1	31 (84%)
Worsened (≥0.3)	0	0	0	0	0	0

Source: Analyzed from Visual Acuity Listing 16.2.6.1 (Study 101), Page 2-13

6.1.11.2 Mobility Testing

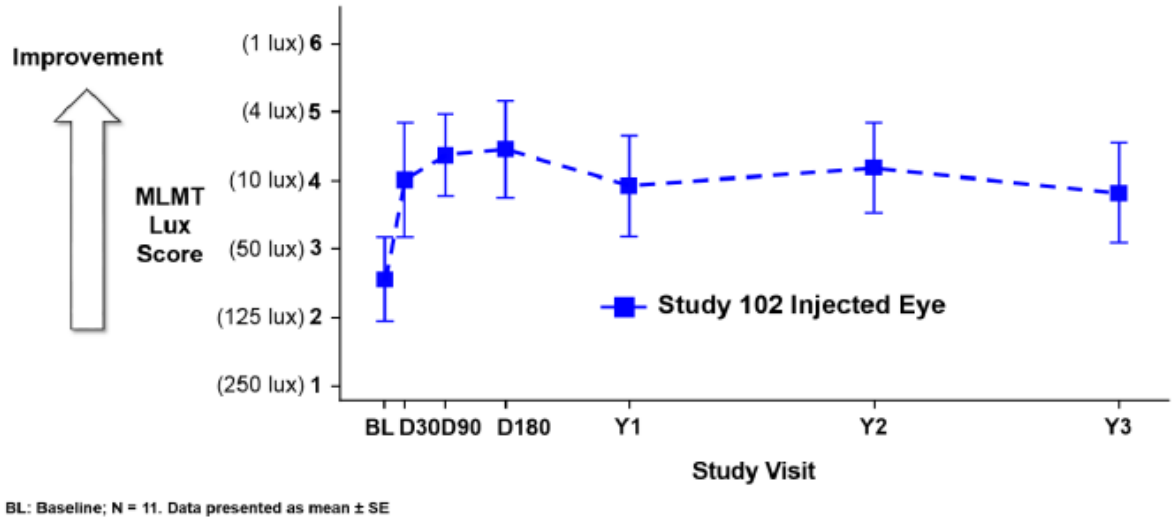
Functional vision was assessed via mobility testing. For the mobility testing, subjects were requested to navigate through a course under certain lighting conditions, following a path defined by large black arrows on the tiles of the floor while avoiding obstacles placed along the path. The performance was timed and videotaped.

During the course of Study 101, the mobility test was further refined and standardized (see Section 2.5), which affected both the number of subjects considered evaluable and the interpretation of the results. Three (43%) of the 7 subjects from CHOP showed some improvement in mobility testing when using the treated-eyes as compared with baseline. None of the untreated eyes showed any improvement (Listings 16.2.6.14, 16.2.6.15, and 16.2.6.16, Study 101). The mobility test was not set to operate at the Italian site, so that certain subjects did not have follow-up mobility testing conducted.

In Study 102, eight of the 11 subjects showed improvement in the mobility testing suggested by the ability to pass the test at lower luminance levels at different time points over a 3-year follow-up period after voretigene neparvovec administration as compared to the baseline (Figure 3).

Based on the Phase 1 study results, the applicant decided to refine the mobility test (which later evolved into the MLMT) for use as the primary endpoint for the Phase 3 study.

Figure 3. Study 102 Mobility Test Results Over Three Years



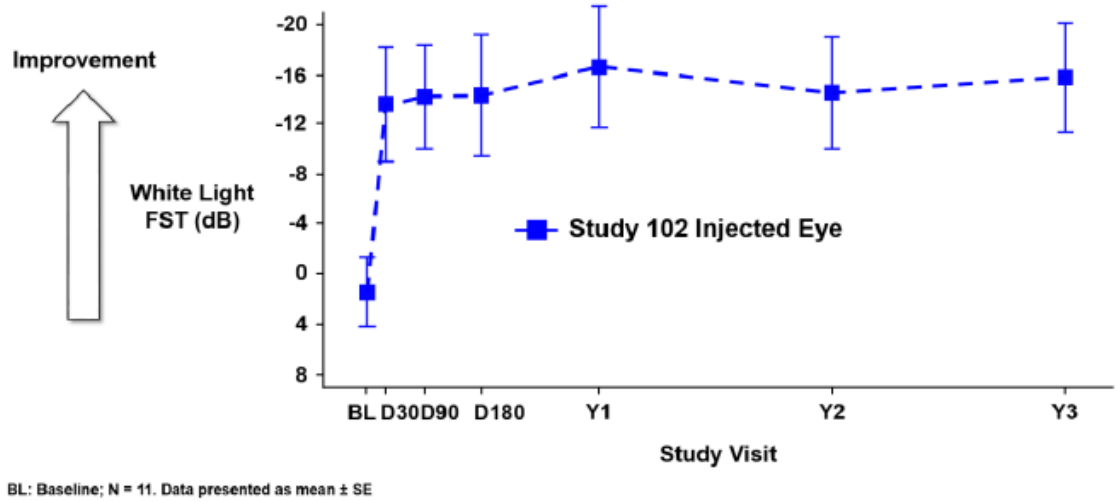
Source: Figure 30, page 73. Spark Therapeutics Briefing Document

6.1.11.3 Full-Field Light Sensitivity Threshold Testing (FST)

FST assesses light sensitivity of the entire retina by measuring the subject's perception of different luminance levels and is a subjective physiological test of retinal function. Pupil dilatation and dark adaptation are needed before the test can be conducted. Each eye is tested individually. When testing commences, light flashes inside the entire dome accompanied by a beeping sound. Each time a beep sounds the subject must indicate whether they saw a light by pressing a "yes" or "no" button. Light flashes continue at different intensities and an algorithm identifies the minimum luminance (brightness) at which the subject reliably perceives light. FST testing is not affected by nystagmus and has an extensive dynamic range, which allows it to be used to evaluate individuals' vision ranging from normal to profound visual impairment. FST testing assesses night blindness, a common clinical manifestation in patients with retinal dystrophy due to mutations in *RPE65* gene. Results are measured in relative units (decibels or dB), which are converted to absolute units (candela second per square meter or cd.s/m2) to allow comparison across sites and subjects. The metric for analysis uses log10 (cd.s/m2).(Source: Applicant's BLA)

The majority of the subjects in Study 102 were able to respond at a lower light intensity following voretigene neparvovec administration. The response started at Day 30 and was sustained over three years as shown in Figure 4. FSA was chosen as the key secondary efficacy endpoint based on the above finding.

Figure 4. FST Testing Results of Study 102 over Three Years



Source: Figure 4, page 17. Spark Therapeutics AC Briefing Document

6.2 Trial #2 (Phase 3, Study 301)

6.2.1 Objectives

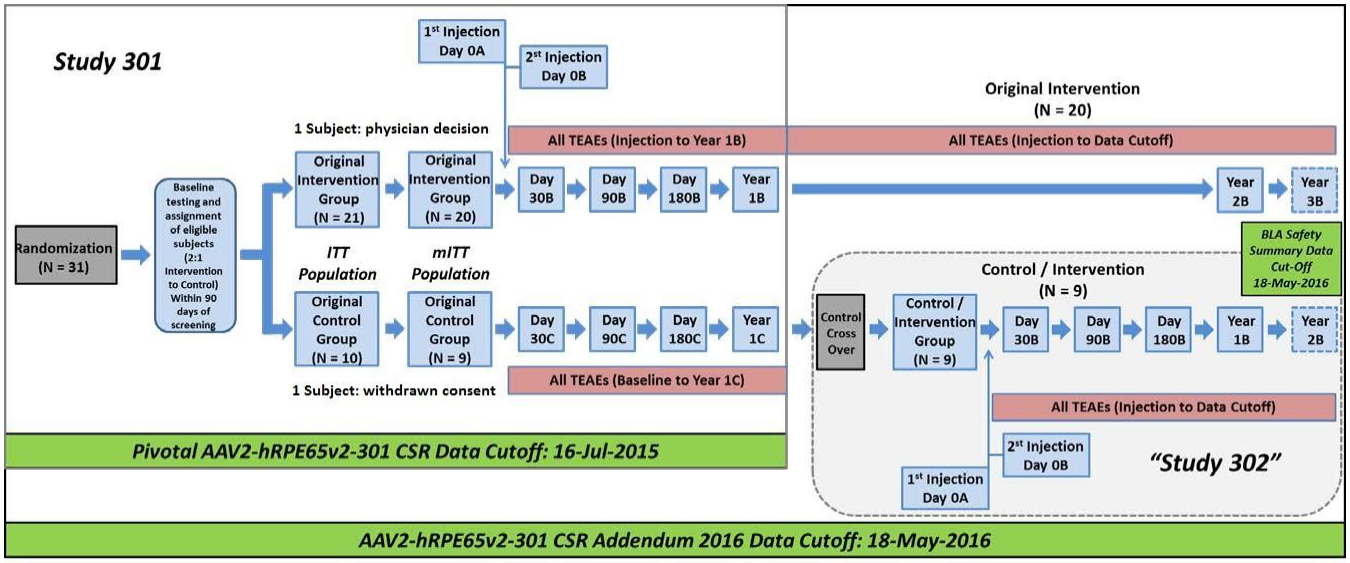
The primary objective of Study 301 was to evaluate the safety, efficacy and tolerability of sequential subretinal administration of voretigene neparvovec to each eye.

6.2.2 Design Overview

Study 301 was an open-label, randomized, controlled Phase 3 study. Thirty-one (31) subjects were randomized in a 2:1 ratio to the treatment (n=21) or the control (n=10) group. Twenty (20) subjects in the treatment group received sequential subretinal injections of voretigene neparvovec to each eye. The injection interval between the two eyes for each subject ranged between 6 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 corticosteroids. However, all the subjects in the control group underwent the same safety and efficacy outcome assessments, including MLMT, as subjects in the treatment group during the one-year study duration period.

After the one-year evaluation, nine (9) of the 10 subjects in the control group of Study 301 crossed over to receive sequential subretinal injections of voretigene neparvovec to the second eye. The injection interval between the two eyes of each subject varied from 7 to 14 days. The applicant refers to this part of the study as "Study 302". The Phase 3 study design is shown in Figure 5.

Figure 5. Phase 3 Study Design



Source: Figure 2.7.4.2 in 2.7.4. Clinical Summary of Safety
CSR: Clinical study report; TEAE: Treatment emergent adverse event

See discussion of the study design in Section 7.1.4.

6.2.3 Population

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

6.2.4 Study Treatment

Dose Regimen

- Intervention: One dose, 1.5 x10^{11} vg/300 µL, was administered by subretinal injection.
- Control: no investigational product or corticosteroids were given.

Product Formulation Used in the Study
Voretigene neparvovec:

- a sterile concentrate for solution for subretinal injection containing 5 x 10^{12} vector genomes (vg) per mL, supplied in a 0.5 mL extractable volume in a single dose 2-mL vial, which requires a 1:10 dilution prior to administration.
- The Diluent, supplied in 1.7 mL extractable volume per vial in two 2-mL vials, is composed of sterile water containing 180 mM sodium chloride, 10 mM sodium phosphate, 0.001% Poloxamer 188 (pH 7.3). After dilution, each dose consists of 1.5 x 10^{11} vg in a deliverable volume of 0.3 mL.

Route and Mode of Administration
Voretigene neparvovec was administered via subretinal injection. See Appendix 13.3 for detailed injection procedure.

Concomitant Use of Corticosteroid
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.

Of note, peri-ocular injection of various corticosteroids used in Phase 1 trial (Section 6.1.4) were discontinued in Phase 3 trial to decrease the incidence and severity of elevated intraocular pressure and cataract formation/progression.

6.2.5 Directions for Use (Device)

Please see Appendix 13.4 for the devices used for subretinal injection.

Reviewer's Comment: Legally marketed devices made of the same or similar material from other device manufactures may also be used for subretinal injection of voretigene neparvovec.

6.2.6 Study Sites

- The Children's Hospital of Philadelphia, Philadelphia, PA (CHOP)
- University of Iowa Hospitals and Clinics, Iowa City, IA (IA)

6.2.7 Surveillance/Monitoring

The schedule of assessment was summarized in Table 19 A for both Study 301 and Study 302. Subjects received voretigene neparvovec at Day 0, followed by the safety and efficacy assessments at Days 30, 90, 180, and one year. The primary efficacy endpoint was assessed at one year following product administration. Subjects in the control group underwent the same assessment at the 4 time points during the first year, and then they were crossed-over to receive the investigational product. The protocol specified a 15-

year follow-up for all subjects (Table 19 B), including five years of annual visits to assess safety and efficacy and ten years of annual phone contact or visit, mainly for clinical questionnaire.

For monitoring of study conduct, see CRO information under Section 6.1.

Table 19 A. Schedule of Assessments Study 301

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

[1] Days -3A and 8B were not study visits. Subjects were to begin taking systemic corticosteroids prescribed following confirmation of eligibility and randomization or crossover to the Intervention group.

[2] Tear collection only.

[3] Ophthalmic exams at these visits were to include OCT and fundus photography.

[4] Ophthalmic exams at these visits were to include visual acuity testing to monitor recovery from surgery.

Source: Table 9.2, Clinical Study Report 301, Page 51

Table 19 B. Schedule of Assessment for Long-Term Follow-Up

Visit Name	Study Visit Description	Assessments

Year 2B to Year 5B	**Study Visit at Administration Site or Referral/Follow-up Site**	• Physical examination, including vital signs
		• Blood and urine tests: About 6 mL of blood will be needed.
		• Ophthalmic examination, including fundus photography and OCT
		• Mobility testing
		• Secondary visual/retinal function testing:
		  ○ Pupillometry
		  ○ Full-field light sensitivity threshold testing
		  ○ Visual acuity tests
		• Additional visual/retinal function testing:
		  ○ Visual field tests
		  ○ Contrast sensitivity testing
		  ○ Visual function questionnaire
		• Clinical questionnaire

Year 6B – Year 15B	**Telephone contact or Study Visit**	• Clinical questionnaire • Visual function questionnaire

6.2.8 Endpoints and Criteria for Study Success

6.2.8.1 Definition of primary and secondary endpoints (in the protocol)

- The primary efficacy endpoint was defined as the mean MLMT score change using both eyes from baseline to one year.

- The secondary endpoints included:

    - Change in full-field light sensitivity threshold testing (FST) using white light, as measured by the averaged FST of two eyes at Year 1;

    - MLMT score change using the first eye from baseline to Year 1;

    - Change in VA as measured by the averaged change in VA of the two eyes at Year 1.

- Safety endpoints included
    - Incidence of adverse events and serious adverse events, which were assessed by adverse event recording, routine physical exams and ophthalmic evaluations, and routine laboratory tests such as serum chemistry and hematology,
    - Immune responses to AAV2 and *RPE65*, assessed by antibodies to AAV and *RPE65*, T-cell responses to AAV2 and RPE65 by ELISPOT assay in PBMCs).

Reviewer's Comment: FDA recommended co-primary endpoints of MLMT score change using both eyes and using the first treated-eye; FDA recommended analyzing each eye separately for FSA and VA instead of using the average values; FDA recommended using ITT for primary analysis instead of using mITT (see Section 2.5).

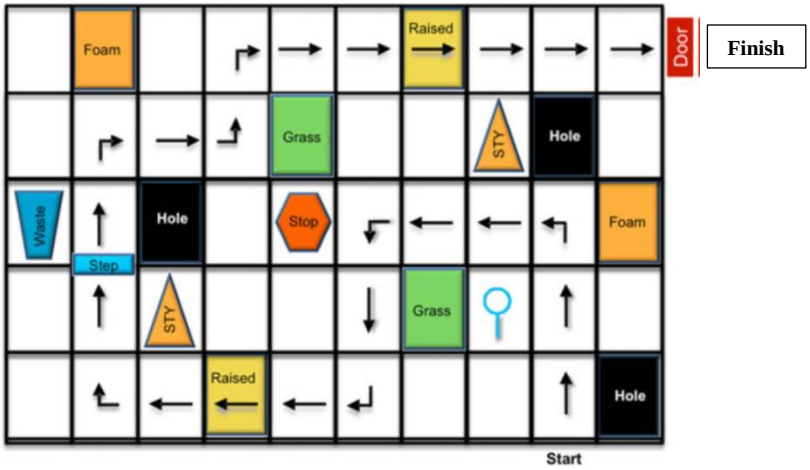
6.2.8.2 Multi-luminance mobility testing (MLMT)

MLMT is a novel endpoint. It was designed 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.

Navigation Course

Figure 6 is an example of the twelve randomized navigation courses designed with the same number of arrows, turns, and obstacles to test the speed and the accuracy of the subject's mobility. This novel test measures the functional vision, i.e., vison-related mobility for subjects with low vision. The size of the course is 5 feet by 10 feet.

Figure 6 Example of the 12 Navigation Courses

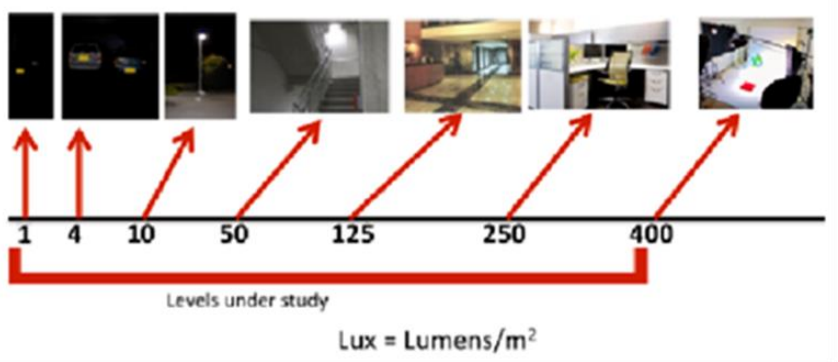


Source: Page 139, Spark therapeutics AC Briefing Document

Lighting condition

The MLMT was conducted using the following seven luminance levels as specified: 1, 4, 10, 50, 125, 250 and 400 lux (Figure 7). The luminance levels were measured in lux within 20% error. The luminance levels were verified with calibrated light meters at 5 different positions on the course. The lowest light level is 1 lux, corresponding to the light level of a moonless summer night; the highest light level is 400 lux, corresponding to the light level of an office environment.

Figure 7. Luminance Levels Used in the MLMT



Source: IND 13408

MLMT performance

The MLMT was performed at screening, baseline, Days 30, 90, 180, and 365. 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 evaluators scored each video. Speed, defined as the time to complete the course, and accuracy, defined as the 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 (Table 20). 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.

Table 20. Lux luminance Level and MLMT Score Code

Luminance Level (Lux)	1	4	10	50	125	250	400	>400
MLMT Score Code	6	5	4	3	2	1	0	-1

Source: Page 67, Module 2.7.3 Summary of Clinical Efficacy

Validation of MLMT (Reference #31)

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 performed the MLMT three times over the one year assessment period. 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 are summarized below.

- 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.

Reviewer's Comment: FDA considered the validation study adequate to support the use of MLMT as a primary endpoint for the Phase 3 study.

6.2.9 Statistical Considerations and Statistical Analysis Plan (SAP)

(Source: FDA Statistical Review)

Before data lock of the Phase 3 trial, FDA had interactions with the applicant to finalize the SAP dated June 30, 2015. Major recommendations included: (1) use of co-primary endpoints, including MLMT score change using both eyes and the first-treated eye instead of the proposed MLMT score change using both eyes; (2) analysis of each eye separately for secondary endpoints, FST and VA, because the proposed average values of both eyes were not clinically meaningful; (3) justification of the clinical meaningfulness of the MLMT score change of one or more; (3) defining the ITT population as all randomized subjects; and (4) the conduct of multiple sensitivity analyses if there are missing data.

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% simulated power to detect an MLMT score change of 1 or more for the 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

The ITT population was specified as the primary analysis population for all efficacy endpoint analyses. The Modified intent-to-treat (mITT) and Per protocol (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. The definitions of the specific population follow:

- Intent-to-treat (ITT) population: all randomized subjects.
- Modified intent-to-treat (mITT) population: all randomized subjects who received treatment
- Per protocol (PP) population: all mITT subjects excluding subjects who did not receive both injections for the treatment group.
- Safety population: all subjects who received at least one injection in either eye.

Analysis of the Primary Efficacy Endpoint: a non-parametric permutation test based on a Wilcoxon rank sum test statistic.

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 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.

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 were to 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 were to be used. If all data were missing for the one year assessments, the Day 180 data were 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.

Note: Efficacy analyses are discussed in Section 7 and Safety analyses in Section 8.

7. OVERVIEW OF EFFICACY

This section provides an overview of efficacy that was derived from the Phase 3 study, the only Phase 3 trial that provides the primary evidence of effectiveness for voretigene neparvovec. There is no integration of data from more than one trial under this section.

Design of the Phase 3 study was described in detail in Section 6 of this review.

7.1 Indication #1

7.1.1 Demographics, Baseline Characteristics, and the Analysis Population

Demographics

Demographics are summarized using the ITT population by study groups in Table 21. Overall, the age of subjects ranged from 4 to 44 years. Twenty subjects were under 18 years of age (20/31, 64%). There were slightly more females (58%) than males (42%). The subjects were primarily white (68%). All other races were represented. The demographics of the two study groups were balanced, except that the treatment group had more pediatric subjects.

Table 21. Demographics (ITT), Study 301

Category	Treatment (N=21)	Control (N=10)	Total (N=31)
Age (Years)			
Mean (SD)	14.7 (11.8)	15.9 (9.5)	15.1 (10.9)
Quartiles (Q_1, Median, Q_3)	6,11,18	9,14,24	6,11,20
Range (min, Max)	4, 44	4, 31	4, 44
Age Groups (Years), n (%)			
4-10	9 (42%)	5 (50%)	14 (45%)
11-17	6 (29%)	0	6 (19%)
>17	6 (29%)	5 (50%)	11 (36%)
Sex, n (%)			
Male	9 (43%)	4 (40%)	13 (42%)
Female	12 (57%)	6 (60%)	18 (58%)
Race, n (%)			
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

Distribution by Age, by MLMT, and by study site

To decrease variation between the treatment and control groups, randomization was stratified by (1) age (<10, ≥10 years) and by (2) baseline MLMT performance (<125, ≥125 lux). Table 22 shows the distribution of subjects between the treatment and the control groups by age groups, and by MLMT performance at baseline. The distribution by study sites is also displayed in Table 22. The baseline feature by age appears balanced between the treatment and the control groups. However, more subjects with better baseline MLMT performance (<125 lux) were enrolled in the treatment group. Regarding the two study sites, fewer subjects were enrolled in the control group at the Iowa (IA) site (20%, 2/10) than at the CHOP site (80%, 8/10). One of the two subjects in the control group at the IA site withdrew consent at the screening visit. Therefore, only one subject from the IA site remained in the control group.

Reviewer's Comment: This imbalance of the baseline MLMT did not seem to impact the interpretation of safety and efficacy significantly. For the safety, the ocular adverse events were related to subretinal injection of product and concomitant systemic corticosteroid use but not related to the MLMT. For the efficacy, better MLMT performance at baseline, such as the four subjects with baseline MLMT score of 5 in the treatment group, may lead to ceiling effect (i.e., the actual magnitude of MLMT score change may be larger than what can be measured). As a result, there may be more subjects in the treatment group who had an MLMT score change of 2 or greater than what is shown in Table 26. As a result, this imbalance did not affect the overall efficacy conclusion. See more discussion in Section 7.1.4.3 d.

The subgroup analyses between the two sites are discussed in Section 7.1.7.

Table 22. Enrollment by Two Strata and By Study Sites (ITT)

Category	Treatment (n=21)	Control (n=10)	All (n=31)
Strata: Age at Screening			
Age<10 years	9 (43%)	4 (40%)	13 (42%)
Age≥10 years	12 (57%)	6 (60%)	18 (58%)
Strata: MLMT at Screening			
Pass at <125 lux	12 (57%)	4 (40%)	16 (52%)
Pass at ≥125 lux	9 (43%)	6 (60%)	15 (48%)
Study site			
Children's Hospital of Philadelphia (CHOP)	11 (52%)	8 (80%)	19 (61%)
University of Iowa (IA)	10 (48%)	*2 (20%)	12 (39%)

Note: *two IA subjects in control group were (b) (6) . (b) (6) withdrew consent at the screening visit due to personal reason.
Source: adapted from Table 10.1, Page 78, 302: Study Body (Admt. 001, Jan 19, 2017)

Study Analyses Population

Table 23 shows a summary of the study analysis populations. The ITT population included all 31 randomized subjects. The ITT population was used for all primary analyses. The mITT population included 29 (94%) subjects who received the treatment, and was used for sensitivity and supportive analyses.

Table 23. Analyses Populations

Category	Treatment N (%)	Control N (%)	Overall N (%)
Randomized	21 (100%)	10 (100%)	31 (100%)
ITT population	21 (100%)	10 (100%)	31 (100%)
mITT population	20 (95%)	9 (90%)	29 (94%)

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

7.1.3 Subject Disposition

Table 24 summarizes subject disposition of the Phase 3 study. Overall, two subjects discontinued the study, one from the treatment group who was discontinued by the PI at the baseline visit due to severe retinal atrophy before the randomization assignment was known, and one from the control group who withdrew consent at the screening visit due to personal reasons. (Source: Case Report Forms of subjects (b) (6)).

Table 24. Subject Disposition for Study 301

Category	Subject Disposition and Reason
Screened	• Total: n =36 • Screen Failures: n=5 o n=2 (a 12-year-old child and a 50-year-old adult failed MLMT criterion at screening visit o n =1 (4 years of age): attention limitation o n=1 (12 years of age): failed VA and VF cut-offs o n=1 (10 years of age): lack of voluntary assent
Randomized (ITT)	• Total: n=31 o Treatment Group: n=21 o Control Group: n=10
Dropout/Discontinuation	• Total: n=2 o Treatment Group: n=1 ((b) (6) , physician decision, severe retinal degeneration; discontinued at baseline visit before receiving treatment) o Treatment Group: n=1 ((b) (6) , subject withdrawal at screening visit due to personal reason)
Treatment (mITT)	• Treatment Group: n=20 • Control Group: n=9
Completion of One Year Assessment	• Treatment Group: n=20 • Control Group: n=9
Cross-over	• Control Group crossed over to receive voretigene neparvovec: n=9 • Completion of one-year assessment: n=9

Source: adapted from Figure 10.1, Page 80, 301 Study Body (Jan 2017). ITT: intention-to-treat population. mITT: modified intention-to-treat population. Case Report Forms of (b) (6)

Reviewer's Comment: The reason for discontinuation of (b) (6) was due to severe retinal atrophy based on OCT although documented retinal thickness by OCT was >100 micron; the subject met the OCT inclusion criterion (right eye=219 micron and left eye=159

micron). This further implies that retinal thickness alone as measured by OCT may not be reliable for selecting the responders (see Section 7.1.4.3.d).

Of Note, Case Report Form (CFR) of (b) (6) (Study 301) stated the reason for discontinuation as "OCT confirmation severe retinal atrophy/degeneration", "in consultation with the medical monitor PI decided to exclude subject (b) (6) on 02 May, 2013 (baseline visit). The PI and medical monitor were not aware of subject's randomization assignment when the decision was made".

7.1.4 Analysis of Primary Endpoint(s)

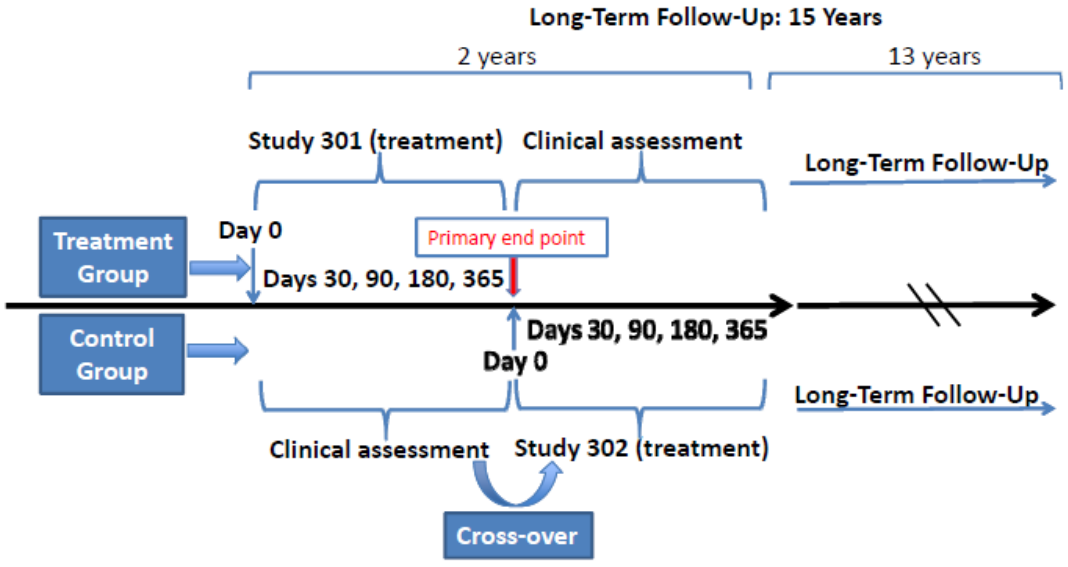
7.1.4.1 Primary endpoint definition

The primary endpoint was defined in the protocol as the performance on the MLMT using both eyes, as measured by the mean MLMT score change, one year following voretigene neparvovec administration as compared to subjects' baseline performance. See Section 2.5 for the evolution of the primary endpoint. See Section 6.1.8 for the description of MLMT.

7.1.4.2 Clinical trial design aspects that impact the interpretation of efficacy of voretigene neparvovec (*Reference #1, 19*)

This subsection discusses different components of the Phase 3 study design that affect the interpretation of the efficacy outcome. Figure 8 briefly summarizes the Phase 3 study design.

Figure 8. Phase 3 Study Design



Source: generated by FDA reviewer

The reviewer provides the following discussion/comments regarding study design:

1. Selection of a control group: the options included a parallel control, a contralateral eye or a historical control. A parallel control group was selected instead of using the contralateral eye or historical data as a control. Internal control with a contralateral eye is generally not appropriate because the treatment eye and the contralateral eye may be at different stages of the disease, and the disease progression between eyes is not necessarily sufficiently similar over one to two years. In addition, both eyes need to be treated to achieve the optimal functional vision. Historical control may be used when the course of the disease is predictable in a defined population and there is a similar group of patients previously studied to serve as the historical control. Like open-label design, historical control is susceptible to bias due to variability of the study populations.

2. Blinding vs. open-label: use of sham-surgery was rejected due to (1) risks associated with general anesthesia and surgical complication of vitrectomy such as infection, and (2) lack of prospective of direct benefit for pediatric participants. To minimize the bias derived from the open-label design, the two evaluators were blinded when scoring the videos of the MLMT performance.

Reviewer's Comment: The use of sham surgery involves greater than minimal risk and provides no prospect of direct benefit to pediatric subjects, so it does not meet the regulatory requirements under 21 Code of Federal Regulation 50, Subpart D.

3. Measures to decrease variation between the treatment and control groups: (1) randomization with stratification by age (<10 vs >10) and MLMT performance at baseline; (2) cross-over of the control group after one year to provide an internal control to compare the MLMT performance for one year before and after the treatment in the same cohort.

4. Sample size consideration: due to the small patient population, a large effect size on a clinical outcome needs to be achieved. Based on the Phase 1 results, 50% of subjects showed improvement in MLMT. With a 2:1 randomization ratio, a total of 24 subjects were estimated to provide nearly 100% simulated power to detect a MLMT score change of 1 or more for treatment group as compared with control group at a two-sided Type 1 error rate of 0.05.

5. Clinical meaningfulness of MLMT score change: the applicant proposed an MLMT score change of 1 or more as clinically meaningful. However, based on the analyses of the primary endpoint and the responder rate at different magnitudes of the score change (see Section 7.1.4.3 b), an MLMT score change of one may represent a background fluctuation occurring in both the treatment and the control groups. Furthermore, as discussed during the AC meeting on October 12, 2017, the design of the MLMT lux score may need to be further improved due to unevenness between some luminance levels. Therefore, the clinically meaningful MLMT score change was considered as two or greater by FDA.

6. Duration of study: the primary endpoint (MLMT) and secondary endpoints (FST and VA) were measured at Year 1 followed by LTFU for a total of 15 years. The duration of study and the time point when the primary and secondary endpoints were measured appear adequate as the effect of MLMT was seen at Day 30 after voretigene neparvovec administration and sustained for 1-2 years. The LTFU continues to collect safety and long-term efficacy, including durability of efficacy.

Reviewer's Comment: It is unknown whether the initial response would occur before 30 days as no MLMT assessment was done before Day 30 following administration (Table 19. Schedule of Assessment Study 301).

7. Number of Phase 3 trials: given the low prevalence of the disease and the significant effects seen in the MLMT in the controlled trial, the single Phase 3 trial is considered sufficient to provide the primary evidence of effectiveness to support the BLA (Reference #1).

8. Dosing regimen: three dose levels were tested in a total of 12 subjects enrolled in the Phase 1 study. There was no clear dose response effect with respect to bioactivity or preliminary efficacy, and no different safety signals were identified in any of the three doses. Therefore, the high dose of 1.5×10^{11} vg with a volume of 300 μL was chosen, considering a higher probability for effectiveness among the three doses.

9. Study population: as compared to the Phase 1 trial, the Phase 3 study included a broader population, including younger subjects (four years of age and older in the Phase 3 study versus eight years of age and older in Phase 1 study), and subjects with less advanced disease (VA no better than 20/60 in Phase 3 study versus VA no better than 20/160 in the Phase 1 study).

Reviewer's Comment: the purpose for modification of the inclusion criteria in the Phase 3 trial is to expand the patient population who are considered suitable for the treatment based on Phase 1 data.

Overall, the Phase 3 trial is considered an adequate and well-controlled efficacy study.

7.1.4.3 Analyses of Primary Endpoint: MLMT Score change

This section provides various analyses of the primary endpoint based on ITT and mITT populations to evaluate the effectiveness of voretigene neparvovec. The analyses are listed below:

- MLMT score change at Year 1, using both eyes and using first-treated eye
- Proportion of subjects with different magnitudes of MLMT score change using both eyes and individual eyes
- Time-course of MLMT score change
- MLMT score change for individual subjects

a. MLMT score change at Year 1 (primary efficacy endpoint)

The results of the primary endpoint are shown in Table 25. Both the mean and the median MLMT score change were significantly different between the treatment and the control groups at Year 1, favoring the treatment group, either using both eyes or using the first-treated eye.

Table 25. MLMT Score Change at Year 1 (ITT)

MLMT Score Change	Treatment (N=21)	Control (N=10)	p-value*
Both eyes			
Mean (SD)	1.8 (1.1)	0.2 (1.0)	-
Quartiles (Q1, Median, Q3)	1, 2, 3	-1, 0, 1	0.001
Range (min, max)	0, 4	-1, 2	-
First-Treated Eye			
Mean (SD)	1.9 (1.2)	0.2 (0.6)	-
Quartiles (Q1, Median, Q3)	1, 2, 3	0, 0, 1	0.03
Range (min, max)	0, 4	-1, 1	-

Two-sided p-value is calculated based on Wilcoxon rank-sum test using an exact number
Source: Modified from original BLA 125610/0; Module 5.3.5.1; CSR, p94

Reviewer's Comment: The mean MLMT score change using both eyes at Year 1 was defined in the protocol as the primary endpoint as navigation through the mobility course using both eyes was representative of a real-world situation. However, MLMT using both eyes may reflect the performance of the better-seeing eye. The MLMT score change using the first-treated eye is more appropriate to reflect the efficacy of a single treated eye. Therefore, FDA considered co-primary endpoint of both the MLMT score change using both eyes as well as the MLMT score change using the first-treated eye. The results demonstrate that there was a significant treatment effect regardless of whether the MLMT score change was evaluated using both eyes or the first-treated eye. Given the small sample size of 31 subjects, the reviewer chose to use the median MLMT score change to assess efficacy. Of note, the median MLMT score change in the treatment group, using both eyes and the first-treated eye was two luminance levels (i.e., an MLMT score change of 2). A score change of 2 is considered clinically meaningful as a two-level change is above the background noise (see next section for further explanation).

b. Proportion of subjects with different magnitudes of MLMT Score Change

Table 26 shows the number and percentage of subjects with different magnitudes of MLMT score change using both eyes from baseline to one year. Eleven subjects or 52% of the treatment group had an MLMT score change of 2 or more. In contrast, only one subject or 10% of the control group had a score change of 2. No subject in the control group had a score change greater than 2. Table 27 shows a similar result for the MLMT score change using individual eyes. Fifteen subjects or 71% of the treatment group had a score change of 2 or more when using each individual eye; while no subjects in the control group had a score change of 2 or more.

Reviewer's Comment: As shown in Table 26, 38% of subjects in the treatment group and 30% of subjects in the control groups showed an MLMT score change of one. An MLMT Score change of one may reflect a learning behavior or background variability when performing the MLMT (see more discussion on 7.1.4.2). Therefore, it is more appropriate to consider that an MLMT score change of two or more to be clinically meaningful.

Table 26. M**agnitudes of MLMT Score Change Using Both Eyes at Year 1 (ITT)**

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

Table 27. Magnitude of MLMT Score Change Using Individual Eyes at Year 1 (ITT)

Change Score	First-Treated Eye (N=21)	Control (N=10)	Second-Treated Eye (N=21)	Control (N=10)	
-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 Review

c. Time Course of MLMT Score Change Using Both Eyes in Study 301 and 302 (mITT)

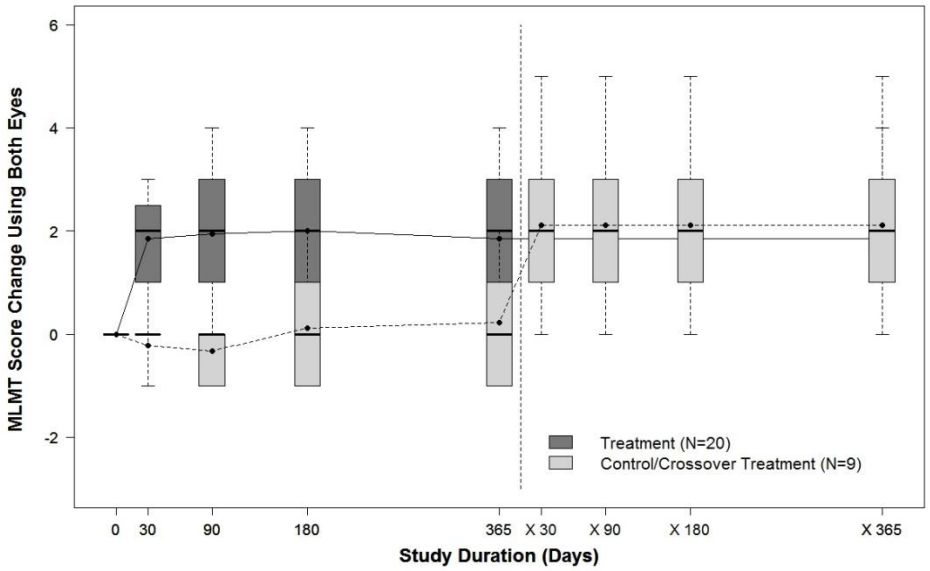
Figure 9 shows the time course of MLMT score changes over two years of observation following voretigene neparvovec administration. A median MLMT score change of 2 was observed for the treatment group at Day 30 after voretigene neparvovec administration and this effect was sustained over the four time points throughout the first year in Study 301 and continued for one additional time point at Year 2. In contrast, a median score change of 0 was observed for the control group for all the follow−up visits during the first year in Study 301.

Figure 9 also shows the MLMT score change for the nine subjects who were crossed over to receive subretinal injection of voretigene neparvovec sequentially in each eye in Study

302 after one year of observation. As shown in the box plot on the right in Figure 9, a median score change of 2 was observed on Day 30 after voretigene neparvovec administration and sustained throughout the one-year period.

Reviewer's Comments: The control group in Study 301 not only served as a parallel control for the treatment group but also served as an internal control for itself after crossing over to receive voretigene neparvovec in Study 302. Similar treatment responses were observed in Study 301 and Study 302. Furthermore, the sustained MLMT score change of two throughout two years in the treatment group of Study 301 supports that the effect of voretigene neparvovec lasts at least two years, which was described in the PI..

Figure 9. MLMT Time-Course Over Two Years: Using Both Eyes

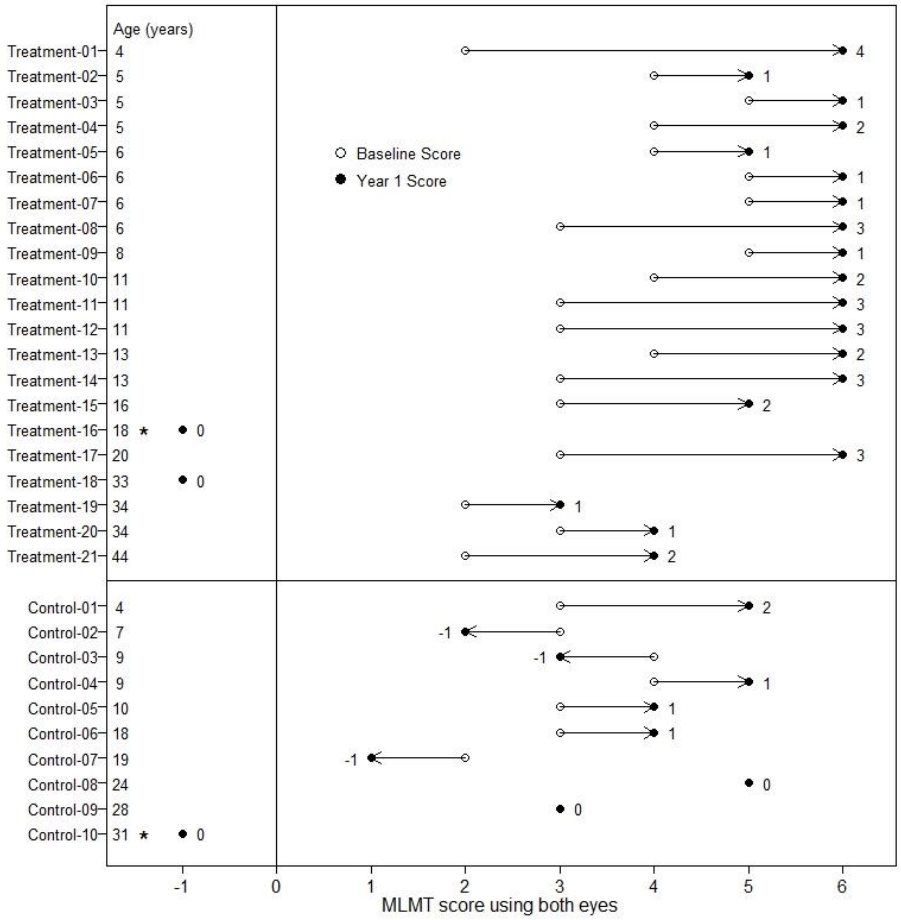


Note: Each box represents the middle 50% of distribution of MLMT score change. Vertical dotted lines represent additional 25% above and below the box. The horizontal bar within box represents the median. The dot within each box represents the mean. The solid line connects the mean MLMT score changes over visits for the treatment group, including five visits during the first year and one visit at Year 2 (marked as x365). The dotted line connects the mean MLMT score change over visits for the control group, including five visits during the first year without receiving LUXTURNA, and four visits within the second year (marked as x30, x90, x180, and x365) after crossed-over at Year 1 to receive LUXTURNA.
Source: FDA Statistical Review

d. MLMT Score Change for Individual Subjects

Figure 10 shows MLMT performance of individual subjects using both eyes at baseline and at Year 1. Eleven out of the 21 subjects in the treatment group shifted to the right with an MLMT score change of 2 or more; in contrast, 1 out of the 10 subjects in the control group shifted to the right with an MLMT score change of two. Of note, in the treatment group, four out of the eight subjects who had an MLMT score change of one may be affected by a ceiling effect, because their baseline score of 5 was only one light level below the maximum value on the scale.

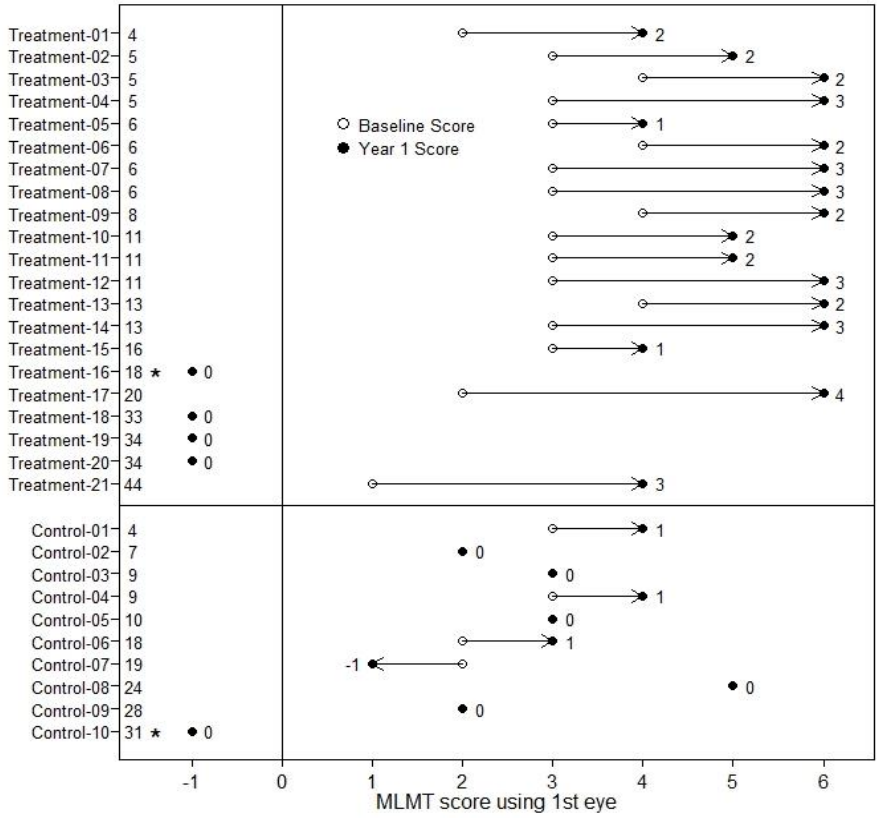
Figure 10. MLMT Score Change for Individual Subjects Using Both Eyes (ITT)



Note: *subjects who were withdrawn or discontinued. MLMT score = -1: failing the test at 400 lux light level. The open circles are the baseline scores. The closed circles are the one year scores. The numbers next to the solid circle represent score change at Year 1. The horizontal lines with arrows represent the magnitude of the score change and its direction. Arrows pointing toward right represent the improvement. The top section shows the results of the 21 subjects in the treatment group. The bottom section shows the results of the 10 subjects in the control group. Subjects in each group are chronologically organized by age, with the youngest subject at the top and the oldest subject at the bottom.
Source: FDA Statistical Review

A similar result is seen when using the first-treated eye (Figure 11). Fourteen out of the 21 subjects in the treatment group shifted to the right with an MLMT score change of 2 or more. No subject in the control group had an MLMT score change of 2 or more. Of note, three subjects, identified as Treatment-18, -19, and -20 in Figure 11, had MLMT scores of -1 at both baseline and Year 1 (i.e., these subjects could not complete the navigation course at the highest light level of 400 lux), and an MLMT score change of 0 when using the first-treated eye. To identify the potential reasons for the unresponsiveness of these three subjects, the reviewer analyzed the correlation of MLMT with FST (Figure 12). (See further discussion in Section 7.1.5 a)

Figure 11. MLMT Score Change for Individual Subjects Using First-Treated Eyes (ITT)



Source: FDA Statistical Review

Reviewer's Comment: multiple analyses of the MLMT results, including MLMT performance from baseline to one year, MLMT performance at different time points throughout two years, responder rates as well as MLMT performance of individual subjects, showed significant improvement in the treatment group compared to the control group. These results are also consistent with the 3-year data from the earlier mobility testing results from the Phase 1 trial (see Section 6.1.11).

OCT measurement of retina thickness was used to identify patients who may respond to voretigene neparvovec. However, 3 of the 20 subjects, who were enrolled based on the OCT criterion, failed to respond to voretigene neparvovec. Therefore, it is not appropriate to use the retinal thickness measured by OCT to identify patients who may respond to treatment. The OCT can measure the thickness of retina; however, it may not inform treating physician whether there are viable retinal pigment epithelial cells.

7.1.5 Analysis of Secondary Endpoints

As specified in the statistical analysis plan, since the primary endpoint was statistically significant, the secondary efficacy endpoints were tested hierarchically in the following order.

a. 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
b. MLMT with first-treated eye (analysis was discussed in conjunction with the primary endpoint in Section 7.1.4)
c. Visual acuity (VA): change in visual acuity (averaged over both eyes) at one year as compared to baseline.

a. Full-Field Light Sensitivity Threshold (FST) Testing

Full-field light sensitivity threshold testing assesses light sensitivity of the entire retina by measuring the subject's perception of different luminance levels. FST testing is not affected by nystagmus; therefore, it allows evaluating individuals either with lesser degrees of impairment or with profound visual disability. During the exploration in Phase 1, a majority of the subjects showed improvement in FST. As FST testing measures retina light sensitivity related to night blindness experienced by patients with *RPE65* mutation-associated retinal dystrophy, FST was chosen as the first key secondary endpoint.

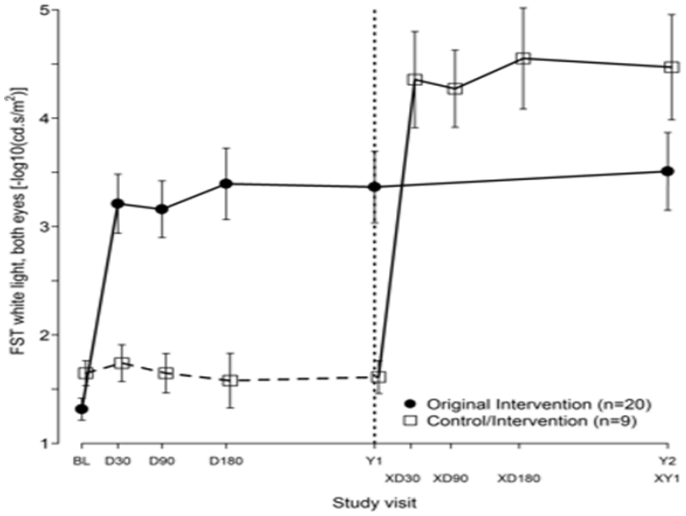
In the Phase 3 study, analysis of white light FST testing using either the first-treated eye or the second-treated eye showed statistically significant improvement from baseline to Year 1 in the treatment group compared to the control group (Table 28). FST improvement was noted at Day 30 and sustained for two years (Figure 12).

Table 28. White Light FST Testing [Log10 (cd.s/m2)] at Year 1

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

Source: FDA Statistical Review (Modified from original BLA 125610/0; Module 5.3.5.1; CSR, p112, 114 and 115)

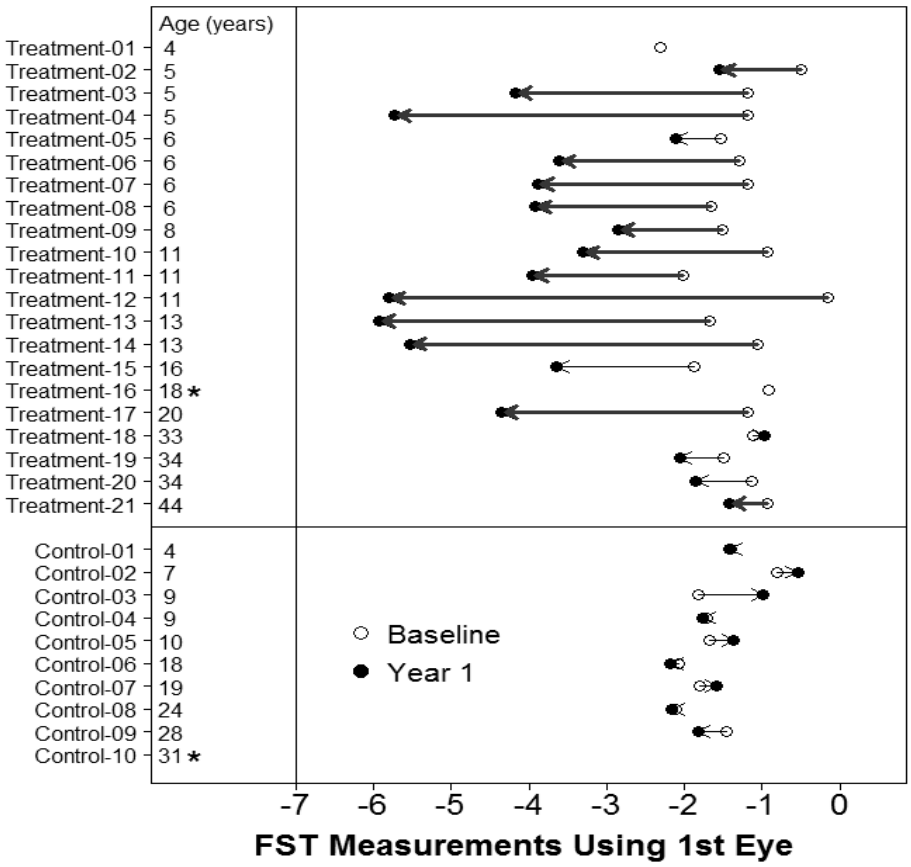
Figure 12. Observed Mean FST White Light Testing Over Two Years in Study 301/302 (mITT)



Note: BL: baseline. Intervals are +/- one standard error. P-value <0.001 (first year of study)
Source: Figure 36, Page 90, Spark Therapeutics AC Briefing Book

Figure 13 below shows the mean FST testing results for individual subjects using the first-treated eye at baseline and at Year 1. Twelve or 57% (12/21) of the subjects in the treatment group shifted to left (improvement) by two or more units (ranging from 2-6 units), while none of the subjects in the control group had more than one unit of improvement. The FST results are consistent with the MLMT results using the first-treated eye (Figure 9 and Figure 12). Four subjects (Treatment -5, -18, -19, and -20 in Figure 11) who failed to improve in the mobility testing with an MLMT score change of 0 or 1 had an improvement in FST testing of no more than 1 unit (≤1 unit). Only one subject (Treatment -21) who had less than one unit improvement on FST had three luminance-level of improvement on MLMT.

Figure 13. FST Testing [Log10(cd.s/m^2)] Outcome for Individual Subjects at Year 1



Note: *: subjects who were withdrawn or discontinued. There was no one-year data for Treatment-1. The open circles are the baseline values. The closed circles are the one-year values. The horizontal lines with arrows represent the magnitude of change at Year 1and its direction. Arrows toward left indicate improvement. The top section shows the results of the 21 subjects in the treatment group. The bottom section shows the results of the 10 subjects in the control group. Subjects in each group are chronologically organized by age, with the youngest subject at the top and the oldest subject at the bottom.
Source: FDA statistical review

Reviewer's Comment: the results of the FST testing corroborate and support the results of MLMT. However, the direct clinical benefit of FST is not clear.

b. Visual Acuity (VA)

Visual acuity is a traditional measure of central visual function, particularly the ability of the eye to perceive details and is primarily cone-mediated. VA is the most common measure of visual function both in clinical practice as well as in clinical trials. In patients with retinal dystrophy due to biallelic *RPE65* mutations, VA is often severely impaired early in life.

Early Treatment of Diabetic Retinopathy Study (ETDRS) VA test chart, the most commonly used VA measurement in clinical studies, was used for most subjects in the Phase 3 study. VA results are presented in logarithm of the minimum angle of resolution (LogMAR) units allowing for comparison analyses, 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 ETDRS eye chart. Change of VA of 0.3 LogMAR is considered clinically meaningful (per communication with CDER ophthalmology consultant). For subjects who were unable to correctly identify the largest line of letters on the chart, off-chart VA measurements were collected (*i.e.,* counting fingers, hand motion perception, light perception, no light perception) and were assigned a LogMAR value using the scale adapted from Holladay (see Table 29 for reference).

A summary of VA results is shown in Table 29. The change in visual acuity from baseline to Year 1 was not statistically significant different between the treatment and the control groups when analyzed for VA averaged over both eyes (pre-specified in the protocol) or for the analyses of VA data using first- and second-treated eyes separately.

Table 29. Visual Acuity change at Year 1 (Holladay*, LogMAR) Phase 3

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

Source: FDA statistical review (Modified from original BLA 125610/0; Module 5.3.5.1; CSR, p112, 114 and 115). *: Holladay (2004). "Visual Acuity Measurements." J Cataract Refract Surg 30 (2): 287-290.

FDA reviewers conducted additional exploratory analyses of visual acuity. As shown in Table 30, there were trends towards improvement based on the number and percentage of subjects with visual acuity improvement of LogMAR 0.3 in each eye. A visual acuity improvement of LogMAR 0.3 occurred in 11 subjects, or 55% of the first-treated eyes, and 4 subjects, or 20% of the second-treated eyes. However, no subject in the control group had a visual acuity improvement of LogMAR 0.3 in either the first or second-treated eyes.

Reviewer's Comment: although the mean change of VA at Year 1 did not reveal statistical significance between the study groups, the exploratory analysis suggests that more subjects in the treatment group achieved clinically meaningful VA improvement, which may provide some basis for improvement in the MLMT. Some level of visual acuity may be needed to see the arrows on the floor of the course and to pass MLMT with acceptable accuracy and speed.

Table 30. VA Improvement of LogMAR 0.3 in Treatment and Control Groups at One Year * (Phase 3)

Study 301 (mITT)	First-treated eye (0.3 LogMAR)	Second-treated eye (0.3 LogMAR)
Treatment Group (n=20)	11 (55%)	4 (20%)
Control Group (n=9)	0 (0%)	0 (0%)

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

7.1.6 Other Endpoints: exploratory efficacy endpoints

7.1.6.1 Visual Field

Visual field was tested in the Phase 3 trial as an exploratory endpoint. Visual field measures the peripheral retinal function while the eye is focused on a central point. Visual field loss leads to an inability to detect peripheral objects with a reduced ability to avoid obstacles, which is one of the common manifestations in patients with retinal dystrophy due to *PRE65* mutations.

In the Phase 3 trial, Goldmann perimetry (assessing the full extent of the visual field for each eye; frequently used in low vision patients and those with nystagmus) as well as Humphrey computerized testing (evaluating the sensitivity of specific points in the central retina [macula and fovea]) were tested. Goldmann VFs were reported as sum total degrees that the subject was able to perceive across all 24 meridians. The maximal visual field is 1200 to1400 sum total degrees in individuals without visual impairment. Humphrey testing is reported in decibels (dB) for both fovea and macula threshold. For both sum total degrees and decibels, a higher number means improvement.

As shown in Table 31, both methods of visual field testing, Goldmann (full extent of visual field) and Humphrey (central threshold) supported visual field improvement at Year 1.

Table 31. Visual Field Outcome at Year 1 (Phase 3)

Measurement	Mean Difference (95% CI) (Intervention-Control)	p-value
Goldmann III4e, sum total degrees, averaged over both eyes	378.7 (145.5, 612.0)	Nominal p = 0.006
Humphrey, mean macula threshold, dB, averaged over both eyes	7.9 (3.5, 12.2)	Nominal p < 0.001

Source: adapted from Table 5, page 25, Spark therapeutics Briefing Document

Reviewer's Comment: the result of the VF testing is consistent with the results of MLMT and FST and is supportive of the overall efficacy of voretigene neparvovec. Of

note, change of 7 decibels is considered clinically meaningful, per CDER ophthalmology consultant.

7.1.6.2 Visual Function Questionnaire and Community-based Functional Vision Assessments (Orientation and Mobility, O&M)

Visual Function Questionnaire

Visual function questionnaire was developed by National Eye Institute of NIH. It is a patient-reported outcome (PRO) suitable for individuals with extremely poor vision. It consists of 25 questions pertaining to activities of daily living that depend on vision or have a vision component. Subjects and parents responded about the perceived difficulty of these activities on a zero (0) to ten (10) numerical scale (zero being the most difficult). The average of the responses determines the numerical score for each subject. As reported by the applicant, the mean score of the treatment group increased, indicating a reduction in the perceived difficulty in activities of daily living, while the mean score of the control group did not change in the first year.

Reviewer's comment: this is a PRO with intrinsic subjectivity and susceptibility to bias. The results should be interpreted with caution.

Community-based Functional Vision Assessments

Community-based functional vision assessments, Orientation and Mobility (O&M), were conducted yearly in the Phase 3 trial, although no formal analysis was planned. These narratives or case studies provide a "visual ability profile" which may be useful as a representation of actual visual performance in everyday life and activities of daily living. Four skilled, trained evaluators performed yearly (baseline, one-year and two-year follow-up) assessments in the subject's home environment and surrounding area, and the same evaluator (masked to randomization assignment) performed all assessments on a given subject.

A total of 87 assessments were reviewed for the mITT population in 29 subjects. The assessments consisted of specific questions and tasks that enabled the evaluator to determine various visual abilities within the areas of basic visual skills, illumination, O&M observed tasks, mobility, and observed tasks related to activities of daily living.

As reported by the applicant, subjects who had improvements in the community-based functional assessments also showed improvements in MLMT performance.

Reviewer's comment: The functional vision assessment is subject to bias. The results should be interpreted with caution.

7.1.7 Subpopulations

This section provides an overview of the efficacy analyses in specific subpopulations. The purpose of comparisons of subpopulations of interest is to evaluate the observed

clinical effect across all groups and to show whether the claimed clinical effects are consistent across all relevant subpopulations, especially in subpopulations of special interest, such as pediatric and geriatric subpopulations.

Table 32, Table 33, Table 34 and Table 35 show the subgroup analyses by age, sex, race, and study sites using the ITT population, respectively. The subgroup analyses were consistent with the overall primary efficacy analysis in favor of voretigene neparvovec.

As no geriatric subjects aged 65 and above were enrolled in the study, there are no efficacy data for geriatric population.

Reviewer's Comment: In the 20 pediatric subjects (14 subjects aged 4 to10 years and 6 subjects aged from 11 to17), no clinically meaningful differences in efficacy were observed between the two pediatric subgroups (4 to 10 years of age and 11 to 17 years of age).

The subgroup analysis by sex was consistent with the primary efficacy analysis.

It is challenging to interpret the subgroup analysis results by race as there were few subjects of other races other than White.

Table 32. MLMT Score Change Using Both Eyes by Age at Year 1 (ITT)

Age Groups (Years)	Treatment (N=21)	Control (N=10)
4-10		
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
11-17		
N	6	0
Mean (SD)	2.5 (0.5)	--
Quartiles (Q1, Median, Q3)	2, 3, 3	--
Range (min, max)	2, 3	--
>17 (adult, no upper limit)		
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 33. MLMT Score Change Using Both Eyes by Sex at Year 1 (ITT)

Sex	Treatment (N=21)	Control (N=10)
Female		
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
Male		
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 34. MLMT Score Change Using Both Eyes by Race at Year 1 (ITT)

Race	Treatment (N=21)	Control (N=10)
White		
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
Asian		
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
American Indian or Alaska Native		
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
Black or African American		
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 35. MLMT Score Change Using Both Eyes by Study Site at Year 1 (ITT)

Study Sites	Treatment (N=21)	Control (N=10)
Children's Hospital of Philadelphia		
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
University of Iowa Hospitals and Clinics		
N	10	2
Mean (SD)	1.9 (1.0)	0 (NA)
Quartiles (Q1, Median, Q3)	1, 4	0, 0
Range (min, max)	1, 2, 2	0, 0, 0

Source: FDA statistical reviewer's analysis

7.1.8 Persistence of Efficacy

In the Phase 3 trial, the effect of voretigene neparvovec was first documented at the first follow up visit (Day 30) after voretigene neparvovec administration and sustained for two years in the 21 subjects in the treatment group. It is not clear whether the initial response occurred before 30 days as MLMT was not assessed before 30 days following voretigene neparvovec administration.

A long-term follow-up for up to 15 years is ongoing for the 41 subjects in the Phase 1 and Phase 3 studies to continue collecting information for long-term safety and efficacy. Based on data submitted in this BLA, the persistence of efficacy of voretigene neparvovec was documented for a duration of two years (Phase 3). See Section 7.1.4.3 for more discussion.

7.1.9 Product-Product Interactions

As there are no approved pharmacological products for the proposed indication, product-product interactions with approved products are not applicable to the discussion. Systemic and topical corticosteroids were used as concomitant medications to suppress potential immune reactions to AAV2 viral capsid and RPE65 proteins; however, there were no observed interactions for the concomitant use of corticosteroids and voretigene neparvovec.

7.1.10 Efficacy Conclusions

The following summarizes the efficacy of voretigene neparvovec:

1) Efficacy database: the primary evidence of efficacy came from 31 subjects in the Phase 3 trial.

2) The primary endpoint was met based on primary and secondary analyses using ITT and mITT populations:

a. A significant difference in the median MLMT score change was noted between the treatment and the control groups, favoring the treatment group, when using either both eyes together or the first-treated eyes;
b. An MLMT score change of 2 (i.e., an improvement of 2 light levels) was seen at Day 30 and sustained throughout the one-year follow-up period.
c. An MLMT score change of 2 (improvement of 2 light levels) or greater occurred in 52% of the subjects in the treatment group compared to 10% of the subjects in the control group when using both eyes;
d. An MLMT score change of 2 or greater occurred in 71% of the subjects in the treatment group compared to zero subjects in the control group when using individual eyes.

3) Results of key secondary endpoints are consistent with the results of the primary endpoint:
    a. There was a significant difference in FST testing between the treatment and the control groups, favoring the treatment group.
    b. Although there was no statistically significant difference in visual acuity between the treatment and the control groups at Year 1, there was a trend towards improvement favoring the treatment group in the exploratory analysis.

Reviewer's Comment: The limitations of the Phase 3 trial included: small sample size, a single Phase 3 trial, open-label design, and imbalanced baseline of MLMT performance. However, the study design and conduct offset the limitations in the following areas: concurrent control, cross-over design, blinded evaluators for MLMT, overall balanced demographics and baseline characteristics between the treatment and the control groups, and low discontinuation rate in each group and limited missing data.

8. INTEGRATED OVERVIEW OF SAFETY

This section discusses the safety findings from both Phase 1 (Study 101 and Study 102) and Phase 3 (Study 301 and Study 302) studies (Refer to Section 6 for study design of each trial).

8.1 Safety Assessment Methods

For the integrated review of safety, the safety database of both Phase 1 and Phase 3 studies were pooled together with a total sample size of 41 subjects. Overall, subject demographics and exposure to voretigene neparvovec were similar in both Phase 1 and Phase 3 trials.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Safety population includes all subjects who received voretigene neparvovec in at least one eye. Safety database included the following:

- Total number of subjects: 41 subjects, 81 eyes

- Phase 1: 12 subjects, 23 eyes
- Phase 3: 29 subjects, 58 eyes

Length of the safety data collection:

- Phase 1 (data cut-off on May 18, 2016):
  - Study 101, injection of the first-treated eyes), n=12: six years between the first-treated subject and data cut-off
  - Study 102: injection of the second-treated eyes), n=11: three years of cumulative data
- Phase 3 (data cut-off on May 18, 2016)
  - Study 301, injection of bilateral eyes in the treatment group, n=20: two years of cumulative data
  - Study 302, injection of bilateral eyes of crossed-over subjects (control group in Study 301), n=9: one year of cumulative data

8.2.2 Overall Exposure and Demographics of Pooled Safety Populations

Table 36 shows the overall exposure to voretigene neparvovec in both trials. Forty subjects received subretinal injection of voretigene neparvovec sequentially to both eyes. One subject received injection to only one eye. A total of 72 eyes were exposed to the high dose of $1.5x10^{11}$ vg in 300 µL injection volume. Three eyes were exposed to the low dose of $1.5\ x10^{10}$vg in 150 µL injection volume, and six eyes were exposed to the medium dose of $4.8\ x10^{10}$vg in 150 µL injection volume.

Table 36. Overall Exposure to Voretigene Neparvovec in Phase 1 and Phase 3

	$1.5\ x10^{10}$vg In 150 µL (n)	$4.8\ x10^{10}$vg in 150 µL (n)	$1.5x10^{11}$ vg In 300 µL (n)	All Subjects (n)	All Eyes
Study 101 (first eye)	3	6	3	12	12
Study 102 (second eye)	-	-	11[a]		11[a]
Study 301 intervention (both eyes)	-	-	20[b]	20[b]	40
Study 302 (cross-over to treat both eyes)	-	-	9	9	18
Total	3 eyes	6 eyes	72 eyes	41 subjects	81 eyes

[a]: One subject was not eligible for Study 102 due to glaucoma; this subject's second eye did not receive treatment

[b]: One subject in the treatment group was discontinued early (see Section 7.1.3) and did not receive treatment; one subject in the control group withdrew consent

Source: Adapted from Table 2.7.4.2 Module 2.7.4. Clinical Summary of Safety

Table 37 shows the demographics of the pooled safety population. The average age of the 41 subjects was 17 years, ranging from 4 to 44 years. Of the 41 subjects, 25 (61%) were pediatric subjects who were 17 years of age and younger. Fifty-six percent (56%) of the subjects were females. Seventy-six percent of the subjects were White, 12% were Asian, 7% were American Indian or Alaska Native, and 5% were Black or African American.

Table 37. Demographics of the Safety Population

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

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

8.2.3 Categorization of Adverse Events (AEs)

All AEs analyzed in the safety database were treatment-emergent adverse events. These AEs were recorded after Day 0 (treatment day) and were tabulated by MedDRA (Medical Dictionary for Regulatory Activities) system organ class and preferred term.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Table 38 shows the similarity and differences between Phase 1 and Phase 3 study populations and the exposure to voretigene neparvovec. Overall, the demographics of the two trials are similar. Exposure and treatment intervals are different between the two trials. The Phase 1 subjects were exposed to different doses and treated at longer intervals between the two eyes. The subjects in the Phase 1 study received higher doses of corticosteroids (oral, subtenon, and subconjunctival) than the subjects in the Phase 3 study.

Reviewer's Comment: overall, due to the similarity between the Phase 1 and Phase 3 trial and the small sample size, the pooling of the safety data should not adversely affect the identification and analysis of the safety data.

Table 38. Comparison of Patient population and Study Treatment between Phase 1 and Phase 3 trials

Study Population and Exposure	Phase 1 (n=12)	Phase 3 (n=29)
Demographics (age, pediatric subgroup, gender, race)	Similar	Similar
Disease stage at baseline	Severe	Moderate to severe
Exposure to voretigene neparvovec	Three different doses to first-treated eyes; high dose to second-treated eyes	High dose to all eyes
Concomitant Drug	Systemic + intraocular corticosteroid	Systemic corticosteroid only
Treatment interval between two eyes	1.7-4.6 years	6-18 days (n=20, treatment, Study 301) 7-21 days (n=9, cross-over, Study 302)

Source: generated by the reviewer

8.4 Safety Results

8.4.1 Deaths

There were no deaths in any of the clinical studies.

8.4.2 Nonfatal Serious Adverse Events (SAEs)

There were eight SAEs in seven subjects. Four SAEs, including anal fistula, increased intraocular pressure ((b) (6)), cryptorchism, and paresthesia, occurred in the Phase 1 study. Four SAEs, including convulsion (baseline refractory seizure), adverse drug reactions (two events, adverse reaction to general anesthesia in an oral surgery) and retinal disorder ((b) (6) , foveal thinning and loss of vision), occurred in the Phase 3 study. The two ocular SAEs with severe consequences were considered by FDA to be related to treatment. The details of these two ocular SAEs are shown in Table 39.

Reviewer's Comment: the intraocular infection is a rare complication of vitrectomy. The reviewer attributes the persistent elevated intraocular pressure to local steroid administration used to treat inflammation. No immune reactions were identified in this case. Following this AE in this Phase 1 study subject, the applicant discontinued the use of intraocular steroids in the protocol, and recommended the use of systemic corticosteroids for treating inflammation.

Foveal thinning and loss of central vision in the second subject was related to the subretinal injection in this subject with pre-existing atrophy of the retina. Nonetheless, this subject had a large improvement in visual function under dim illumination conditions and was able to ambulate independently at night where she had been unable to before. This improvement has been sustained despite the loss of central vision.

The two SAEs represent the risks associated with the surgical procedure, which are adequately addressed in the Prescribing Information. Measures to mitigate these risks include use of the aseptic surgical technique and surgical training.

Table 39. Serious Ocular Adverse Events

Subject	Age, gender	Study	Events	Outcome
(b) (6)	21 year-old, male	102*	• Endophthalmitis at Week 4; vitreous culture positive for staphylococcus epidermidis, treated with antibiotics and periocular steroids • Elevated IOP between Days 90 - 180 associated with periocular steroids use • 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
(b) (6)	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: modified from 2.7.4.2.3: Narratives; Module 2.7.4: Clinical Summary of Safety

8.4.3 Study Dropouts/Discontinuations

- N=1 dropout from Study 301 control group: subject withdrew consent.
- N=1 discontinuation from Study 301 treatment group: due to severe retinal atrophy, subject was discontinued by investigator before receiving voretigene neparvovec (see Section 7.1.3)

No subject was discontinued due to adverse events.

8.4.4 Common Adverse Reactions

8.4.4.1 Treatment Emergent Adverse Reactions

Table 40 lists the incidence of adverse reactions among all subjects in the Phase 1 and Phase 3 studies. The most common ocular adverse reactions occurring in > 5% safety population were conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, eye inflammation, macular hole, retinal deposit, eye irritation, eye pain, and maculopathy. Twenty-seven (27/41, 66%) subjects in the clinical studies had ocular adverse reactions that involved 46 injected eyes (46/81, 57%). All adverse reactions are considered to be related to the treatment, i.e., voretigene neparvovec, the vitrectomy and subretinal injection procedure, and/or the concomitant use of corticosteroids. Two subjects (22%) in the control group (n=9) of the Phase 3 trial (Study 301) had ocular adverse events (photopsia, contusion of eye ball) as compared to 12 subjects (60%) in the treatment group (n=20) who had ocular adverse events.

Table 40. Ocular Adverse Reactions in Phase 1 and Phase 3 Studies

Adverse Reactions	Subjects n=41	Treated Eyes n=81
Any ocular adverse reaction	27 (66%)	46 (57%)
Conjunctival hyperemia	9 (22%)	9 (11%)
Cataract	8 (20%)	15 (19%)
Increased intraocular pressure	6 (15%)	8 (10%)
Retinal tear	4 (10%)	4 (5%)
Dellen (thinning of the corneal stroma)	3 (7%)	3 (4%)
Macular hole	3 (7%)	3 (4%)
Subretinal deposits*	3 (7%)	3 (4%)
Eye inflammation	2 (5%)	4 (5%)
Eye irritation	2 (5%)	2 (2%)
Eye pain	2 (5%)	2 (2%)
Maculopathy (wrinkling on the surface of the macula)	2 (5%)	3 (4%)
Foveal thinning and loss of foveal function	1 (2%)	2 (2%)
Endophthalmitis	1 (2%)	1 (1%)
Fovea dehiscence (separation of the retinal layers in the center of the macula)	1 (2%)	1 (1%)
Retinal hemorrhage	1 (2%)	1 (1%)

*Transient appearance of a ring-like deposit at the retinal injection site 1-6 days after injection without symptoms
**A macular pucker, also known as epiretinal membrane, is scar tissue formed on the macula.
Source: Modified based on Table 2.7.4.9, Module 2.7.4: Clinical Summary of Safety

8.4.4.2 Review of literature for vitreoretinal surgery complications and anesthesia complications for ocular diseases *(Reference 34, 40, 45, 50; www.uptodates.com)*

Vitreoretinal surgery refers to any surgical procedure that treats eye problems involving the retina, macula, and vitreous fluid. Examples of these disorders include macular degeneration, retinal detachment, and diabetic retinopathy. Routine practice includes vitrectomy such as pars plana vitrectomy, and retinal surgery such as retinal detachment repair and macular hole repair.

Common complications following vitreoretinal surgery include:

- Intraocular bleeding (subretinal, vitreretinal, and suprachoroidal hemorrhage) with a risk of 0.17-1.9%
- Elevation of IOP and glaucoma: IOP elevation early in postoperative period is reported with an incidence of 33-52%. If left untreated, elevation of IOP may cause glaucoma and visual field loss.
- Iatrogenic retinal tear: Most retinal tears are caused by pulling of vitreous due to adherence of retina at the vitreous base.
- Cataract: The most frequent complication associated with pars plana vitrectomy. It appears within days of the surgery. Risk factors include extensive surgical

manipulation, high fluid flow, and repetitive fluid/gas exchange.

- Macular hole: This is a group of disorders with partial or full-thickness defect in the fovea with visual disturbance from mild distortion to poor acuity. It may be due to traction of vitreous during the surgery.
- Endophthalmitis: Postvitrectomy endophthalmitis is an uncommon but serious complication. The incidence is reported at 0.046% after par plana vitrectomy. Gram-positive bacteria are identified in 75-95% of reported cases. A significant portion of the cases remain culture negative. Often the microorganism was introduced during the intraocular surgery due to patients' own flora.
- Sympathetic opththalmia: progressive sight threatening intraocular inflammation, which develops in the second eye after penetrating injury. Incidence is 0.03/100,000.
- Iatrogenic phototoxicity: well-circumscribed white lesions involving the outer retina several disc diameters in size in the macula, within a few weeks, the whitening is gradually replaced by pigmentary mottling of the retinal pigment epithelium. It is caused by the operating microscope as well as the endoilluminator.
- Air-fluid exchange complications: One such complication is damage to the retina associated with air infusion. Another complication during air-fluid exchange is mechanical trauma to the optic nerve head.

Anesthesia for vitreoretinal surgery includes regional anesthetic block and general anesthesia. Anesthetic complications include:

- Retrobulbar anesthesia complications such as globe penetration in 0.08% to 0.71% (n=4000)
- Hemorrhage due to needle-based technique intramuscular injection (local anesthetic)
- Nitrous Oxide: The use of nitrous oxide during general anesthesia by the anesthesiologist in subsequent surgical procedures can lead to intractable elevation of IOP and an eventual central artery occlusion.
- Systemic complication due to spread of local anesthetic into central nervous system

Reviewer's Comment: The types and frequencies of ocular adverse reactions that occurred in the Phase 1 and Phase 3 trials are typical of the ophthalmologic surgical procedure as discussed above.

8.4.5 Clinical Test Results

Frequent laboratory abnormalities observed during the studies are listed below.

- Hyperglycemia (n=5)
- Hypoglycemia (n=6)
- Increased blood creatinine (n=8)
- Mild to moderate leukocytosis (n=20)

Hyperglycemia and leukocytosis may be secondary to perioperative systemic corticosteroid use.

8.4.6 Systemic Adverse Events

Most common systemic adverse events were hematuria (n=9), vomiting (n=13), nausea (n=14), pyrexia (n=17), and headache (n=21).

8.4.8 Adverse Events of Special Interest

1. Endophthalmitis**:** Intraocular infection occurred in one eye of an adult subject following subretinal injection of voretigene neparvovec. *Staphylococcus epidermidis* grew in the vitreous culture. The clinical course was further complicated by glaucoma, cataract, and permanent vision loss due to optic atrophy (see Section 8.4.2).

2. Permanent vision loss**:** Permanent vision loss occurred in two subjects in the clinical trials. One subject is described above. Another adult subject lost central vision of one eye due to permanent macular thinning after subretinal injection of voretigene neparvovec (se Section 8.4.2).

3. Retinal abnormalities**:** Retinal abnormalities related to the subretinal injection of voretigene neparvovec in the clinical trials included retinal tear, macular hole, foveal thinning, loss of foveal function, epiretinal membrane, macular pucker, foveal dehiscence, and retinal hemorrhage. A total of 12 subjects (29%, 12/41) developed these retinal abnormalities.

4. Increase in intraocular pressure**:** Increased intraocular pressure was observed in eight subjects (20%, 8/41) after subretinal injection of voretigene neparvovec. Intraocular pressure was normalized after treatment with topical medications in all but one eye.

5. Cataract: Sixteen events of cataract were reported in nine subjects (22%, 9/41) in the clinical trials. Elective cataract extraction procedures were performed for seven of the 16 events. Other cataracts were not electively extracted. Of note, patients with inherited retinal dystrophy have an increased incidence of cataract formation as compared to the general population, and vitrectomy is associated with an increased incidence of cataract formation and/or progression.

6. Adverse reactions due to systemic corticosteroid use**:** The use of systemic corticosteroids to suppress potential immune reactions to AAV capsid and RPE65 protein in the perioperative period can be associated with leukocytosis, weight gain, dizziness, insomnia, and increased blood glucose; however, these are temporary.

7. Subretinal deposit: The three observed cases of subretinal deposits were possibly related to the specific lot of voretigene neparvovec. All three subjects received voretigene neparvovec from the same lot. The first lot of voretigene neparvovec was administered to 34 subjects and none of these subjects developed retinal deposit. The second lot was administered to 7 subjects (four subjects under the

age of 18 and three subjects aged 18 years or older). Three of the seven (43%) subjects who received the second lot developed retinal deposits and all three were under the age of 18. All three of these events were mild in intensity, transient in nature, and resolved spontaneously without sequelae. No action was required.

Reviewer's comment: Communication with CMC reviewer regarding these cases of the retinal deposits did not reveal any manufacturing deviation or abnormality of the lot release information. To further control the paticulate matter in the injection solution that may cause the deposit, CMC Postmarketing Commitments include the tests for particulate matter for the Drug Product and Diluent (see Section 4.1)

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

In the Phase 1 study (Study 101), three doses were explored in the first-treated eyes of the 12 enrolled subjects.

- Low dose (1.5×10^{10}vg/150µL): n=3
- Medium dose (4.8×10^{10}vg//150µL): n=6
- High dose: (1.5×10^{11}vg//300µL): n=3

There was no clear pattern noted in the types and frequencies of the adverse events among the three dose groups based on review of adverse events listing (Table 14.3.1.1 and Table 14.3.1.2, Page 18-22; Appendix 1 Study 101, Tables/Figures/Listings). The small number of subjects in each dose cohort limits the interpretation of the results.

8.5.2 Time Dependency for Adverse Events

Table 41 lists the ongoing ocular AEs as of May 2016. Most of the adverse events were cataract and macular abnormalities. Most of these AEs occurred after one year of the product administration, consistent with progression of the disease with or without the impact of the treatment. Most of the ongoing AEs can be managed within the context of routine medical practice.

Table 41. Ongoing Ocular Adverse Reactions as of May 2016

Subjects#, Study	Event	Onset to Injection (Days) 1st eye, 2nd eye
(b) (6) , 301	Maculopathy (L)	400, 386
(b) (6) , 301	Maculopathy (R)	400, 386
(b) (6) , 301	Cataract (L)	205, 198
(b) (6) , 301	Intraocular pressure increase (L)	22, 15
(b) (6) , 301	Cataract (L)	386, 379
(b) (6) , 301	Cataract (R)	386, 379
(b) (6) , 301	Cataract (R)	399, 392
(b) (6) , 301	Cataract (L)	414, 407
(b) (6) , 101	Macular hole (R)	15 (1st eye)
(b) (6) , 102	Maculopathy (R)	755 (2nd eye)

Source: modified from Table 2.7.4.7, Module 2.7.4: Clinical Summary of Safety

8.5.8 Immunogenicity (Safety)

A safety concern for AAV vector-mediated gene therapy is the potential immune response (humoral and/or cellular) against the vector, and/or the expressed transgene. Such immune responses can result in inflammation, significant reduction or abrogation of *in vivo* gene expression, or destruction of transduced cells. The immune response can occur in patients who have pre-existing immunity to the vector or as a result of re-administration of the gene therapy product.

To minimize the potential immune responses to voretigene neparvovec, oral prednisone was given before and after voretigene neparvovec administration. To monitor the immune responses, the following tests were performed at baseline and at Days 14 (only Phase 1), 30, 90, and 365 (only Phase 3) after voretigene neparvovec administration:

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

As shown in Table 42 and Table 43, at all doses evaluated in Phase 1 and Phase 3 studies, immune reactions have been mild, even with sequential administration to each eye. In the Phase 1 study (n=12), the interval of sequential subretinal injection of voretigene neparvovec to each eye ranged from 1.7 to 4.6 years. In the Phase 3 study (n=20), the interval of sequential bilateral administration of voretigene neparvovec to each eye was 6 to 18 days. There were limited cytotoxic T-cell responses to either AAV2 vector capsid or transgene product *RPE65* in any of the subjects. There was no inflammatory response, other than occasional transient mild redness and inflammation of the eye (a known common occurrence after ocular procedures), which was not specific.

Table 42. Assessment of Humoral Immune Response

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

Source: adapted from Section 2.7.4.4 Cell-mediated and humoral immune responses with modification

Table 43. Assessment of Cellular Immune Response

Tests	Study 101 (n=12)	Study 102 (n=11)	Study 301 (n=21)	Study 302 (n=9)
Human PBMC Interferon-γ Responses to AAV2 and RPE65 by ELISPOT at baseline, Days 14, 30, and 90	No T cell response to AAV capsid and RPE65	Six subjects with low response at single time point	Two subjects with low response at single time point and one subject with medium response at single time point	Three subjects with low response[(a)], 1 subject with medium response[(b)], and 1 subject with high response e[(c)]

(a) Two subjects had low response at single time point at Year 1C (Year 1C time point is baseline, i.e., prior to vector injection.). One subject low response at two time points (Year 1C, Day 30B).
(b) One subject had medium response at single time point (at baseline, Year 1C)
(c) One subject had high response at two time points (Day 30B and 90B). The same subject had medium responses at baseline, Year 1C.

Source: adapted from Section 2.7.4.4 Cell-mediated and humoral immune response with modification

8.5.9 Person-to-Person Transmission, Shedding

Vector shedding and biodistribution were investigated in a study measuring vector DNA in tears from both eyes, from serum, and whole blood of subjects in the Phase 3 clinical study as shown in Table 44.

Table 44. Summary of Phase 3 Vector Shedding and Biodistribution Data

Category	Total N = 29
Subjects with Any Positive Samples	14 (48%)
Subjects with Only Positive Tear Samples	11 (38%)
Subjects with Only Positive Serum Samples	1 (3%)
Subjects with Both Positive Tear and Serum Samples	2 (7%)

Note: No whole blood samples were positive for AAV2-hRPE65v2 vector DNA.
Source: CSR Phase 3

In 29 subjects who received bilateral administration of voretigene neparvovec, vector DNA was present in tear samples of 13 subjects (45%). Peak levels of vector DNA were detected in the tear samples on Day 1 post-injection, after which no vector DNA was detected in most the subjects (8 of 13). Three subjects (10%) had vector DNA in tear samples up to Day 3 post-injection, and two subjects (7%) had vector DNA in tear samples for around two weeks post-injection. In another two subjects (7%), vector DNA was detected in tear samples from the uninjected (or previously injected) eye until Day 3 post-injection. Vector DNA was detected in the serum of 3/29 (10%) subjects, including two with vector DNA in tear samples up to Day 3 following each injection. In summary, vector was shed transiently and at low levels in tears from the injected eye in 45% of the subjects in the Phase 3 study, and occasionally (7%) from the uninjected eye until Day 3 post-injection.

Reviewer's Comment: The above information was confirmed with the CMC reviewer. No significant immunogenicity was noted following administration of voretigene neparvovec.

8.6 Safety Conclusions

In summary, the safety database included 41 subjects (81 eyes) from the Phase 1 (n=12) and the Phase 3 (n=29) studies. Demographics were similar for both studies but subjects in the Phase 1 study were exposed to three different doses of voretigene neparvovec, had worse baseline visual function, and had longer treatment intervals between the two eyes. Of the 41 subjects, 25 (61%) were pediatric subjects. The most common adverse events were ocular events related to the subretinal injection of voretigene neparvovec and the concomitant use of systemic corticosteroids. These AEs include conjunctival hyperemia, increased intraocular pressure, cataract, retinal abnormalities (retinal tear, macular hole, macular pucker, foveal thinning, retinal bleeding, foveal dehiscence), endophthalmitis, and loss of vision. Most of these events were temporary and responded to medical management. There were ongoing adverse events, including maculopathy, cataracts, and increased intraocular pressure. Two serious ocular adverse events included (1) a case of endophthalmitis with a series of complications as a result of the infection and the treatment; and (2) a case of loss of vision due to foveal thinning as a result of subretinal injection separating already dystrophied retina. Systemic adverse events included hyperglycemia, hypoglycemia, nausea, vomiting, and leukocytosis. These systemic events were likely caused by systemic corticosteroid use and reactions to anesthesia.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

This section provides justification for the content of the Prescribing Information (PI) with regard to special populations. The subsections are organized in parallel with the content of the PI, focusing particularly on the data (or lack of data) regarding each specific population (see Section 11.5).

9.1.1 Human Reproduction and Pregnancy Data

There were no safety or efficacy data for pregnant women in clinical trials. Animal reproductive studies were not conducted.

Reviewer's Comment: Information was confirmed with preclinical reviewer.

9.1.2 Use During Lactation

There was no information regarding the presence of voretigene neparvovec in human milk, the effects on the breastfed infant, or the effects on milk production.

Reviewer's Comment: Information was confirmed with preclinical reviewer.

9.1.3 Pediatric Use and PREA Considerations

(Reference 3 and 11)

PREA is not applicable to voretigene neparvovec for treatment of biallelic RPE65 mutation-associated retinal dystrophy because the indication has been granted orphan designation (see Section 2.5). The clinical trial population included 61% pediatric subjects.

Safety Evaluation of Pediatric Subjects

The safety of voretigene neparvovec was evaluated in pediatric subjects in both Phase 1 and Phase 2 trials. The clinical trials included 25 (61%, 25/41) pediatric subjects with biallelic *RPE65* mutation-associated retinal dystrophy. Table 45 shows the ocular adverse events displayed separately for the pediatric (<18) and adult (≥18) populations. Across the Phase 1 and Phase 3 trials, adult subjects had more ocular adverse events. Among these events, more adults had cataracts, increased intraocular pressure, and macular abnormalities than pediatric subjects. Only pediatric subjects had retinal tear and subretinal deposits. Of note, the interpretation of these safety results is limited by the small sample size of the overall population and in each subgroup.

Table 45. Ocular Adverse Events in Pediatric and Adult Population

Study	301		101		102		All	
Adverse Events in Age Groups	<18 n=20	≥18 n=9	<18 n=5	≥18 n=7	<18 n=5	≥18 n=6	<18 n=25	≥18 (n=16)
cataract	1	3		1	1	2	2 (8%)	6 (38%)
Increased IOP	2	3		1	1	1	3 (12%)	5 (31%)
*Macular abnormality	2	2		1	1		3 (12%)	3 (19%)
Retinal tear	3		1				4 (16%)	
Retinal deposit	3						3 (12%)	
Retinal hemorrhage		1						1 (6%)
Foveal thinning and loss of foveal function								
Foveal dehiscence								
Endophthalmitis		1						1 (6%)
Choroidal hemorrhage		1						1 (6%)
Eye inflammation	1	1			1		2 (8%)	1 (6%)
Retinal disorder		1		1				2 (13%)
Optic atrophy						1		1 (6%)

*Macula abnormality include macular hole, macular degeneration, and maculopathy. Some subjects had more than one adverse event.
Source: Modified from Tables 2.7.4.13 and 2.7.4.14, Page 60-71; Module 2.7.4 Clinical Summary of Safety

Efficacy Evaluation of Pediatric Subjects

The efficacy results in the 20 pediatric subjects (15 in the treatment group and 5 in the control group) were compared to the 11 adult subjects (6 in the treatment group and 5 in the control group). No meaningful differences were noted between pediatric and adults subjects with respect to efficacy. The subgroup analyses are consistent with the overall primary efficacy analysis (Table 32).

9.1.5 Geriatric Use

There are no data on geriatric use as clinical studies for this indication did not include subjects age 65 years and over.

10. CONCLUSIONS

The primary evidence of efficacy is generated from 31 subjects in the Phase 3 study. The study met its primary endpoint (mean and median MLMT score change from baseline to Year 1). Additional robust analyses of the primary endpoint confirm the positive results. The positive primary endpoint results were supported by the secondary efficacy outcome measures.

The safety database included 41 subjects (81 eyes), from the Phase 1 (n=12) and Phase 3 (n=29) studies. The major risks of voretigene neparvovec are associated with subretinal administration of voretigene neparvovec and concomitant oral corticosteroid use. These

risks can be mitigated by routine medical management, adequate PI, and the postmarketing plan proposed by the applicant.

Based on the review of the submitted data, voretigene neparvovec appears safe and effective for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Voretigene neparvovec is expected to improve functional vision that is clinically meaningful in the intended patient population.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Summary and Assessment

As summarized in Table 46, biallelic *RPE65* mutation-associated retinal dystrophy is a serious and sight-threatening genetic disorder with an unmet medical need. Voretigene neparvovec can improve patients' ability to navigate under low luminance for at least two years, which is clinically meaningful. The major risks associated with subretinal administration of voretigene neparvovec and concomitant oral corticosteroid use can be mitigated by routine medical management, adequate Prescribing Information (PI), and the applicant's pharmacovigilance plan. The efficacy and safety data in the BLA support a favorable benefit-risk profile for patients with biallelic RPE65 mutation-associated retinal dystrophy.

11.2 Recommendations on Regulatory Actions

Based on the thorough review of the clinical data, this reviewer recommends the approval of voretigene neparvovec for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. The rationale for the recommendation is discussed in .

11.3 Labeling Review and Recommendations

(Reference 5, 6, 7, 9, 11, 12, 13, 16, and 17)

FDA made substantial changes to each section of the Prescribing Information based on the clinical trial data from Phase 1 and Phase 3 studies and AC discussion as well as FDA guidance on labeling. Table 47 summarizes the major changes and the rationales for the changes.

11.4 Recommendations on Postmarketing Actions

(References 8 and 18)

Based on review of the safety data, none of the following are required: a REMS, a safety PMR study, or a safety PMC study. The postmarketing risk mitigation plans proposed by the applicant are acceptable, including product labeling, applicant's pharmacy and surgical training, a registry study as well as an ongoing long-term follow-up for 41 subjects under IND 13408.

Table 46. Risk and Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Retinal dystrophy due to biallelic *RPE65* mutations is associated with many mutations and a variety of clinical diagnoses • Symptoms include early childhood blindness, nystagmus, night blindness, progressive visual field and visual acuity loss, and progression to inevitable blindness in early adulthood. • See Appendix A for Natural History Study	• Represents a group of serious and sight-threatening genetic retinal diseases with inevitable blindness in early adulthood • Majority of the patients (58% and above) have severe forms with early childhood onset and severe visual impairment shortly after birth; a small portion (8%) of patients with some form of retinitis pigmentosa, who start with night blindness followed by gradual visual field loss and blindness.
Unmet Medical Need	• There is no approved pharmacological product for this indication.	• There is unmet medical need for this indication.
Clinical Benefit	• A total of 52% of the subjects (n=21) in the treatment group compared to 10% of the subjects (n=10) in the control group had an MLMT score change of 2 (i.e., an MLMT improvement of two-luminance level) or greater when using both eyes; 71% of the subjects in the treatment group compared to no subjects in the control group had an MLMT score change of 2 or greater when using the first-treated eye. An MLMT score change of 2 or greater is considered clinically meaningful (background fluctuation of one luminance change was noted in control group). Subjects in the control group showed similar responses of two-luminance level improvement after being crossed-over to receive voretigene neparvovec. • Twenty pediatric subjects were evaluated in the Phase 3 study and showed similar efficacy responses to treatment as the overall study population. • Significant improvements in FST were noted. Trends toward improvement in visual acuity were noted. Visual field, an exploratory endpoint, showed improvement favoring treatment. • Durability of the effect was two years based on data from the Phase 3 study; results from the Phase 1 trial suggest durability of effect may be three to five years based on MLMT and FST testing.	• Overall, the evidence is compelling for a clinical benefit based on data from the single adequate and well-controlled study. • Navigation under different lighting conditions with adequate speed and accuracy is clinically meaningful. • An MLMT improvement of two-luminance level or greater in 50% (using both eyes) and 71% (using the first-treated eye) of the subjects is a large effect. • Change of two-light levels or more is considered clinically meaningful • Primary and secondary analyses of the primary endpoint are robust. • Secondary endpoint, FST, further supports the success of MLMT • The limitations of small sample size, open-label design, and a single Phase 3 trial are offset by the use of concurrent controls, blinded assessment of the MLMT, and incorporation of both a parallel and crossover study design. • A second trial is not needed to confirm the efficacy due to the large effect size and robust analyses.
Risk	• Most important safety concerns arise from complications secondary to the surgical procedure, including routine vitrectomy and subretinal injection. • The risks include intraocular infection, permanent loss of vision, retinal abnormalities such as retinal tear and macular holes, elevated intraocular pressure, new cataract formation or progression of existing cataracts.	• Overall, these risks are temporary and manageable within routine medical practice.
Risk Management	The risk management plan includes: • Applicant's own training plan for pharmacists in preparation of the product and for surgeons performing subretinal injections • Applicant's registry study including 40 patients followed for 5 years • 15 year of long-term follow-up of 41 treated subjects under IND	The risks can be mitigated through routine medical management, adequate PI and the postmarketing plan proposed by the applicant without requiring other regulatory measures such as REMS, PMR, or clinical PMC.

Source: Generated by the FDA reviewer

Table 47. Summary of Labeling Review and Recommendation

Section Number and Title	Recommendation and Rationale
1 INDICATIONS AND USAGE	Modify indication statement: • Add class category "adeno-associated virus", • Delete "vision loss" as this is not specific and may not be necessary or may be redundant with "retinal dystrophy"; • Delete the use of OCT to determine viable retinal cells as there is no clear proof that thickness of retina correlates with viability of retinal cells. In addition, four eyes that met the OCT criterion in Study 301 did not improve in MLMT following treatment. Recommend the treating physician(s) decide whether a patient should be treated.
2 DOSAGE AND ADMINISTRATION	• Replace interval of "6-18 days" with "with a close interval but no fewer than 6 days apart" based on Phase 1 and Phase 3 experience where a wide range of interval between 1-4 years was seen in Phase 1 study without significant immune reactions. • Simplify and relocate systemic corticosteroid use to section 2.1 to be part of the Dose. • Number each step and make amplified picture of syringes, and add list of items for administration.
4 CONTRAINDICATIONS	Delete the items and change to None.
5 WARNINGS AND PRECAUTIONS	• Reorganize this section in order of severity of the adverse reactions. • Add risks of cataract and permanent vision loss.
6 ADVERSE REACTIONS	• Revise Table 2 to focus on ocular adverse reactions in a combined population from Phase 1 and Phase 3 for easy reference. • Modify the preamble to include a brief description of the study design and demographics.
7 DRUG INTERACTION	Delete this section. No data available
8 USE IN SPECIFIC POPULATIONS	Modify this section based on pediatric data in Phase 1 and Phase 3 trials, current knowledge of retinal cells, and input from AC discussion.
9 DRUG ABUSE AND DEPENDENCE	Delete this section. No data available.
10 OVERDOSE	Delete this section. No data available.
11 DESCRIPTION	CMC made revision on this section.
12 CLINICAL PHARMACOLOGY	Preclinical made revision on this section.
13 NON-CLINICAL TOXICOLOGY	Preclinical made revision on this section.
14 CLINICAL STUDIES	• Rewrite and simplify this section to focus on Phase 3 and MLMT – the main evidence for efficacy; • Briefly describe FST and VA for their supportive roles.
15 REFERENCES	
16HOW SUPPLIED / STORAGE AND HANDLING	CMC made revision on this section.
17 PATEINT COUNSELING INFORMATION	This section was revised to address the risks directly to patients and to be consistent with Section 5.

Source: generated by the FDA reviewer; Module 1.1.4. Reference 5, 6, 7, 9, 11, 13, 16, and 17

12. REFERENCE

FDA Guidance

1. Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. 1998
2. Guidance for Industry Special Protocol Assessment. 2002
3. Guidance for Industry How to Comply with the Pediatric Research Equity Act. Draft, 2005
4. Guidance for Industry Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events. 2006
5. Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format. 2006
6. Guidance for Industry Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format. 2006
7. Guidance for Industry Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format. 2010
8. Guidance for Industry Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act. 2011
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13 APPENDICES

13.1 Summary of Natural History Study

To guide the development of voretigene neparvovec for treating retinal dystrophy due to *RPE65* mutations, the applicant conducted a natural history study with retrospective chart review of 70 subjects with retinal dystrophy due to *RPE65* mutations (Table 1). In this cohort of subjects with age ranging from 1 to 43 years, patients with mutations in *RPE65* were diagnosed with a variety of clinical conditions/syndromes (76 different diagnoses). The clinical diagnoses included severe and early-onset retinal dystrophy with early childhood blindness such as Leber congenital amaurosis (58%), early-onset severe retinal dystrophy (5%) or severe early-onset retinal dystrophy (7%), or retinitis pigmentosa (8%) featuring night blindness and a gradual vision field loss. Both visual acuity and visual fields of the affected individuals declined with age, leading to total blindness in young

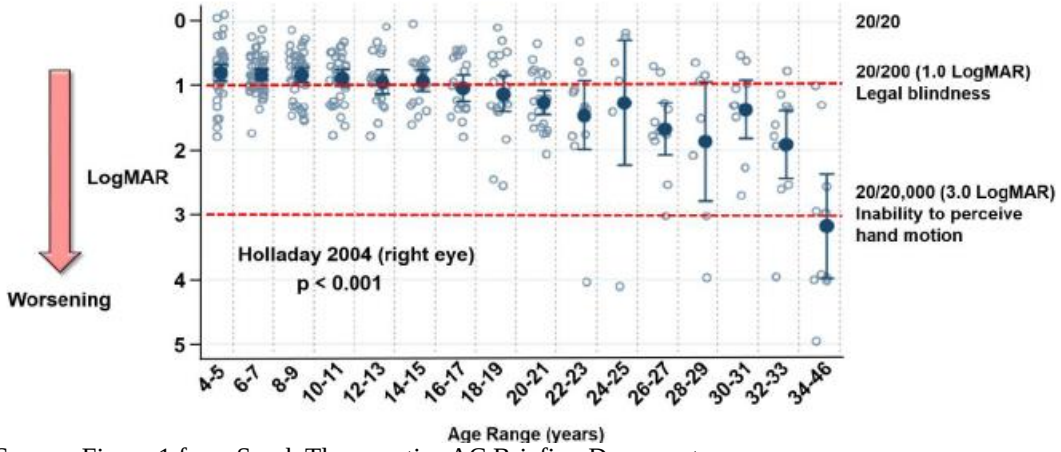
adulthood (Figure 1 and 2).

Table 1. Summary of Natural History Study on Retinal Dystrophy due to RPE65 Mutations

Category	**Description**
Study Design	
Study Sites	7 sites in EU & US
Sample Size	70
Enrollment Criteria	Retinal degeneration due to RPE65 mutations
Clinical data collection	Primary: VA, VF, OCT Secondary: ERG, color vision, ophthalmic exam, ocular history, clinical diagnoses, genotype
Study methods	Retrospective chart review
Study Results	
Age (Years) Gender Race	Mean: 15; Range: 1,43; Median: 9 Female: 42 (60%); male: 28 (40%) Asian: 2 (3%); Black: 14 (20%); white: 47 (67%); other/unknown: 7 (10%)
Clinical Dx (n=76) Genotypes Visual acuity Visual field Other ocular function and structure	• 21 unique clinical diagnoses at the initial visit: o LCA: 58%; o retinitis pigmentosa: 8%; o early onset severe retinal dystrophy: 5%; o severe early-childhood onset retinal dystrophy (SECORD): 7%; o tapetal (sheen or reflection on retina) retinal dystrophy: 14% • 56 unique RPE65 mutations • Non-linear effect of age on VA ($p<0.001$); VA worsened with age with a high degree of variability • a negative relationship between age and visual field for both eyes • worsened with age

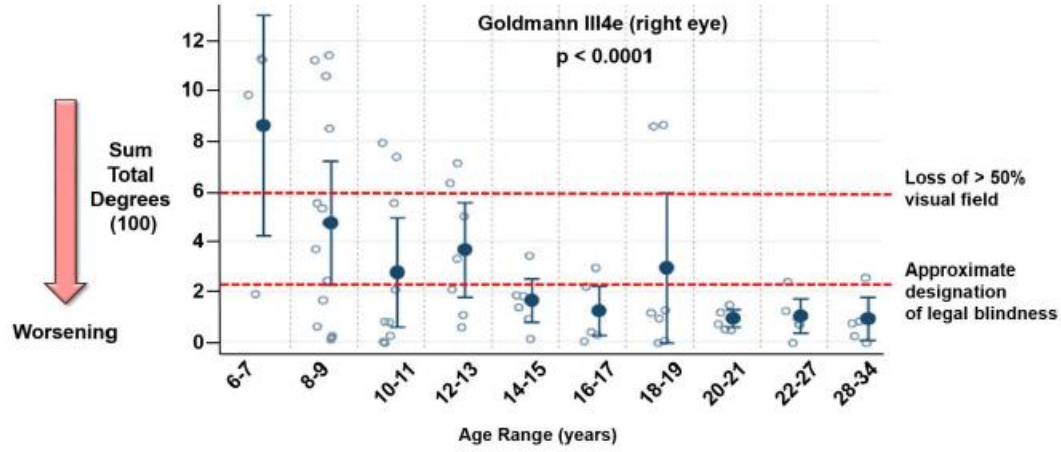
Source: Generated from Study Report of Natural History of Individuals with Retinal Degeneration Due to Autosomal Recessive Mutations in the RPE65 Gene.

Figure 1 Visual Acuity Results in the Natural History Study



Source: Figure 1 from Spark Therapeutics AC Briefing Document

Figure 2 Visual Field Results in the Natural History Study



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

Source: Figure 2 from Spark Therapeutics AC Briefing Document

Individual clinical diagnoses and manifestations are discussed as following:

Leber Congenital Amaurosis (LCA) (Reference 39)

LCA due to RPE65 mutations (LCA2) is the clinical diagnosis for all subjects enrolled in the Phase 1 and Phase 3 trials that support this BLA. Leber congenital amaurosis (LCA), a severe dystrophy of the retina, typically becomes evident in the first year of life. Visual function is usually poor and often accompanied by nystagmus, sluggish or near-absent pupillary responses, photophobia, high hyperopia, and keratoconus. Visual acuity is rarely better than 20/400. A characteristic finding is Franceschetti's oculo-digital sign, comprising of eye poking, pressing, and rubbing. The appearance of the fundus is

extremely variable. While the retina may initially appear normal, a pigmentary retinopathy reminiscent of retinitis pigmentosa is frequently observed later in childhood. The electroretinogram (ERG) is characteristically "nondetectable" or severely subnormal. The birth prevalence of LCA is two to three per 100,000 births, and constitutes more than 5% of all retinal dystrophies. Mutations in at least 17 genes may cause LCA. *RPE65* is one of these genes. Mutations in *RPE65* lead to LCA2 that attributed to 3-16% of all LCA (Reference 39).

Retinitis pigmentosa (RP) (Reference 58)
RP is a group of inherited disorders in which abnormalities of the photoreceptors (rods and cones; affecting rods initially) or the retinal pigment epithelium (RPE) of the retina lead to progressive visual loss. Affected individuals first experience defective dark adaptation or "night blindness," followed by constriction of peripheral visual fields and, eventually, loss of central vision late in the course of the disease. The diagnosis of RP relies on documentation of progressive loss in photoreceptor function by electroretinography (ERG) and visual field testing. Pathogenic variants in more than 50 different genes or loci are known to cause nonsyndromic RP. The prevalence of RP in the US and Europe is approximately 1:3,500 to 1:4,000. RPE65 mutations may attribute 2-5% of all nonsyndromic autosomal recessive retinitis pigmentosa.

Early-onset severe retinal dystrophy and severe early childhood-onset retinal dystrophy (SECORD) (Reference: Orphanet)
Both retinal dystrophy disorders are similar disease entities as LCA, characterized by a severe night blindness, progressive retinal dystrophy and nystagmus. Best corrected visual acuity can reach 0.3 (Snellen) in the first decade of life and can lead to blindness in the second to third decade of life, depending on the underlying gene and mutation.

Tapetal retinal dystrophy
A sheen or reflection on retina (tapetal) was described in various retinal dystrophies such as cone dystrophy and retinitis pigmentosa.

13.2 Molecular Diagnosis

The molecular diagnosis involves conventional single gene sequencing followed by comparison to the published reference gene sequence. The molecular diagnosis is conducted at CLIA (Clinical Laboratory Improvement Amendments of 1988)-Certified high complexity molecular diagnosis Laboratories. The following three laboratories were used for confirming the molecular diagnoses of subjects in Phase 1 and Phase 3 trials.

1. (b) (4)
2. (b) (4)
3. (b) (4)

CLIA oversight for molecular genetic testing involves three government agencies (Table 2), including Centers for Disease Control (CDC), FDA, and Centers for Medicare and Medicaid Services (CMS). Molecular genetic testing is categorized as High Complexity Testing, which must meet regulations on facility administration, quality system requirements for every phase of the testing process, and personnel requirements *(Reference 47).*

Table 2. Government Agencies for CLIA-Certified Laboratories

Agencies	Oversight Responsibility
CMS	To administer the CLIA laboratory certification program in conjunction with FDA and CDC
CDC	To conduct CLIA studies to provide scientific and technical support for CMS
FDA	To provide test categorization for laboratory devices as high or moderate complexity, waived by regulation, or waived by clearance/approval for over-the-counter use. Molecular genetic testing is categorized as High Complexity Testing.

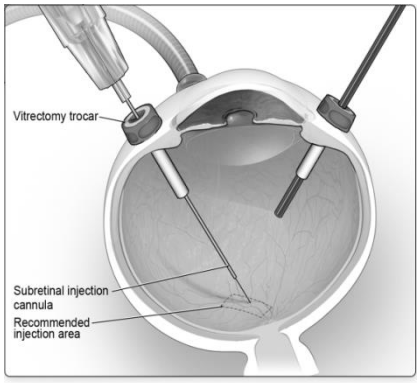
Source: Generated from CDC MMWR Publication (reference #38) and FDA CBER training material for in-vitro diagnosis

13.3 Subretinal Injection Procedures

(Source: Study 301 protocol, Prescribing Information, and Surgical Training Manual)

1. Give adequate anesthesia to the patient prior to administration after confirming the availability of the product from the pharmacy.
2. Dilate the eye to be injected and administer a topical broad spectrum microbiocide prior to the surgery according to standard medical practice.
3. Inspect the product prior to administration. If particulates, cloudiness, or discoloration are visible, do not use the product.
4. Connect the syringe containing the diluted product to the extension tube and subretinal injection cannula (commercially available). The extension tube should not exceed 16 cm in length and 1.4 mm in inner diameter to avoid excess priming volume. Inject the product slowly through the extension tube and the subretinal injection cannula to eliminate any air bubbles.
5. Confirm the volume of product available for injection in the syringe, by aligning the plunger tip with the line that marks 0.3 mL.
6. After completing vitrectomy, administer product by subretinal injection using a commercially available subretinal injection cannula introduced via pars plana (Figure 3).

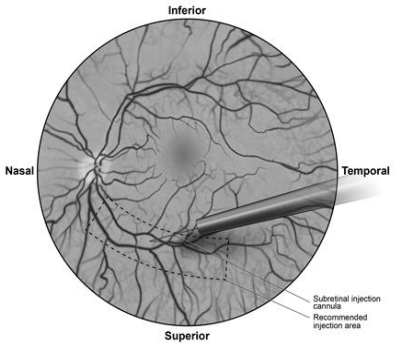
Figure 3 Subretinal injection cannula introduced via pars plana



Source: Draft Prescribing Information

7. Under direct visualization, place the tip of the subretinal injection cannula in contact with the retinal surface. The recommended site of injection is located along the superior vascular arcade, at least 2 mm distal to the center of the fovea, and avoiding direct contact with the retinal vasculature or with areas of pathologic features, such as dense atrophy or intraretinal pigment migration. Inject a small amount of the product slowly until observing an initial subretinal bleb, and then, inject the remaining volume slowly until the total 0.3 mL is delivered (Figure 4).

Figure 4 Tip of the subretinal injection cannula placed within the recommended site of injection (surgeon's point of view)



Note: Tip of the subretinal injection cannula placed within the recommended site of injection at the superior arterial arcade (surgeon's view)
Source: Prescribing Information

8. After completing the injection, remove the subretinal injection cannula from the eye.
9. Following injection, discard all unused product. The back-up syringe may not be retained. Refer to local biosafety guidelines applicable for handling and disposal of the product.

10. Perform fluid-air exchange, carefully avoiding fluid drainage near the retinotomy created for the subretinal injection.
11. Initiate supine head positioning immediately in the post-operative period.
12. Upon discharge, advise patients to rest in a supine position as much as possible for 24 hours.

13.4 Devices used for subretinal injection

Devices used for subretinal injection, including injection cannulas, extension tubes, and syringes, are commercially available and have been tested for biocompatibility with voretigene neparvovec. Names of the device are listed in Table 3 below.

Table 3. Names of biocompatible Subretinal Injection Cannulas and Extension Tubes

Cannula	Extension tube
PolyTip cannula 25g/38g	Ocular irrigation tube 6”
De Juan/Awh subretinal injection cannula 25g/41g	High pressure extension tube
Retinal hydrodissection cannula 20g/39g	

Source: Surgical Training Manual