Summary Basis for Regulatory Action

Date: December 18, 2017

From: Lilia Bi, PhD, Chair of the Review Committee

STN#: 125610

Applicant Name: Spark Therapeutics, Inc.

Date of Submission: May 16, 2017

Goal Date: January 12, 2018

Proprietary Name: LUXTURNA

Proper Name: voretigene neparvovec-rzyl

Indication: for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy.

Recommended Action: The Review Committee recommends approval of this product.

Office of Tissues and Advanced Therapies Signatory Authority:
Wilson W. Bryan, MD, Director

- ☐ I concur with the summary review.
- ☐ I concur with the summary review and include a separate review to add further analysis.
- ☐ I do not concur with the summary review and include a separate review.

Office of Compliance and Biologics Quality Signatory Authority:
Mary A. Malarkey, Director

- ☐ I concur with the summary review.
- ☐ I concur with the summary review and include a separate review to add further analysis.
- ☐ I do not concur with the summary review and include a separate review.

The table below indicates the material reviewed when developing the SBRA

Document title	**Reviewer name, Document date**
CMC Reviews • *CMC (product office)* • *Facilities review (OCBQ/DMPQ)* • *Establishment Inspection Report (OCBQ/DMPQ)*	Lilia Bi, PhD (OTAT/DCGT) Zenobia Taraporewala, PhD (OTAT/DCGT) Robert Aksamit, PhD (OTAT/DCGT) Angela Whatley, PhD (OTAT/DCGT) Denise Gavin, PhD (OTAT/DCGT) Rabia Ballica, PhD (OCBQ/DMPQ) Karla Garcia, MS (OCBQ/DBSQC) Marie Anderson, MS, PhD (OCBQ/DBSQC)
Clinical Reviews • *Clinical (product office)* • *Clinical Consultants Review* • *Clinical Team Lead Review* • *Clinical Branch Chief Review* • *Clinical Division Director Review* • *Postmarketing safety epidemiological review (OBE/DE)* • *BIMO*	Yao-Yao Zhu, MD, PhD (OTAT/DCEPT) Wiley A. Chambers, MD (CDER/OND/DTOP) Bernard P. Lepri, OD (CDRH/ODE/DOED) Changting Haudenschild, MD (OTAT/DCEPT) Lei Xu, MD, PhD (OTAT/DCEPT) Tejashri Purohit-Sheth, MD (OTAT/DCEPT) Bethany Baer, MD (OBE/DE) Adamma Mba-Jonas, MD, MPH (OBE/DE) Carla Jordan, BS, MT (ASCP)SBB (OCBQ/BIMO)
Statistical Review • *Clinical data* • *Non-clinical data*	Min Lin, PhD (OBE/DB) Shiowjen Lee, PhD (OBE/DB)
Pharmacology/Toxicology Review • *Toxicology (product office)* • *Developmental toxicology (product office)* • *Animal pharmacology*	Wei Liang, PhD (OTAT/DCEPT)
Labeling Review • *APLB (OCBQ/APLB)*	Dana Jones, BS (OCBQ/APLB) Oluchi Elekwachi, PharmD, MPH (OCBQ/APLB)
Other Review(s) • *additional reviews not captured in above categories* • *consult reviews*	

1. INTRODUCTION

Spark Therapeutics, Inc. submitted a Biologics License Application (BLA), STN 125610, for licensure of voretigene neparvovec-rzyl. Voretigene neparvovec-rzyl is a new molecular entity, with the proprietary name of LUXTURNA. LUXTURNA is a recombinant adeno-associated virus serotype 2 (AAV2) vector expressing the gene for human retinal pigment epithelium 65 kDa

protein (*hRPE65*), for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy.

The RPE65 protein is expressed in retinal pigment epithelial (RPE) cells and converts all-trans-retinyl ester to 11-cis-retinol, which subsequently forms the chromophore, 11-cis-retinal, in the retinoid visual cycle. Mutations in the *RPE65* gene lead to reduced or absent levels of RPE65 isomerohydrolase activity, blocking the visual cycle and resulting in impairment of vision. LUXTURNA is designed to deliver a normal copy of the gene encoding the human RPE65 to cells of the retina in persons lacking normal function of RPE65.

This document summarizes the basis for regular approval for LUXTURNA. A Phase 1 clinical study and a Phase 3 clinical study provide the primary evidence of safety and effectiveness for the BLA submission. The recommendation for approval is based on the improvement in the multi-luminance mobility testing (MLMT) demonstrated in the Phase 3 study. The more serious risks of LUXTURNA include endophthalmitis (infection inside of the eye), permanent decline in visual acuity, increased intraocular pressure, retinal abnormalities (e.g. retinal tears or breaks), and cataract development and/or progression.

The review team recommends regular approval of this BLA with the Chemistry, Manufacturing, and Control (CMC) Postmarketing Commitments (PMCs) listed in Section 11.c of this document.

2. BACKGROUND

Disease background

Biallelic *RPE65* mutation-associated retinal dystrophy is a serious and sight-threatening autosomal recessive genetic disorder. The visual function, including visual acuity and visual field, of affected individuals declines with age, leading to total blindness in young adulthood. Patients with biallelic *RPE65* mutation-associated retinal dystrophy may be given a variety of clinical diagnoses due to variability in clinical manifestations and ophthalmology examinations. Two common clinical diagnoses that are caused by biallelic mutations in the *RPE65* gene are Leber congenital amaurosis Type 2 (LCA2) and retinitis pigmentosa type 20 (RP20). There are approximately 1,000 to 3,000 patients with biallelic *RPE65* mutation-associated retinal dystrophy in the United States.

Available Therapies

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

The Argus II Retinal Prosthesis System, an implanted device, is approved in the United States under a Humanitarian Device Exemption (HDE). The device is indicated for use in patients 25 years of age and older with severe to profound retinitis pigmentosa (bare light or no light perception in both eyes) by providing electrical stimulation of the retina to induce visual perception.

Regulatory History

Key regulatory milestones in the development of LUXTURNA are summarized in Table 1.

Table 1. Regulatory Milestones

Date	Milestone
9/20/2005	PreIND meeting
6/14/2007	IND 13408 Submission
9/24/2014	Breakthrough Therapy Designation granted
3/25/2016	Pre-BLA meeting
11/29/2016	Orphan Drug Designation granted for the treatment of inherited retinal dystrophy due to biallelic *RPE65* mutation
4/27/2016 2/22/2017 5/16/2017	BLA 125610 Submission (rolling submission) -Preclinical data -Clinical data -CMC data
7/14/2017	BLA 125610 Filed, priority review
7/14/2017	Rare Pediatric Disease Designation granted
10/12/2017	Cellular, Tissue, and Gene Therapies Advisory Committee Meeting
1/12/2018	PDUFA* Action Due Date

*PDUFA=Prescription Drug User Fee Act

3. CHEMISTRY MANUFACTURING AND CONTROLS

a) Product Quality

Product Description

LUXTURNA (voretigene neparvovec-rzyl) 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*), which is an isomerohydrolase converting *all-trans*-retinyl ester to 11-*cis*-retinol in the retinoid visual cycle. Voretigene neparvovec-rzyl is a sterile suspension of non-replicating AAV2 vector at a concentration of 5×10^{12} vector genomes (vg) per milliliter in Water for Injection (WFI) containing 180 mM sodium chloride, 10 mM sodium phosphate, 0.001% (b) (4) P 188®, pH 7.3. The Diluent for voretigene neparvovec-rzyl (Diluent) is an aqueous solution with a formulation identical to the inactive ingredients of the Drug Product, without the active substance. LUXTURNA requires a 1:10 dilution prior to administration. After dilution, each dose of LUXTURNA consists of 1.5×10^{11} vg in a deliverable volume of 0.3 mL.

Manufacturing Summary

The voretigene neparvovec-rzyl Drug Substance (DS) is manufactured by Spark Therapeutics, Inc. The manufacturing process is based on cell culture and transient transfection of adherent human embryonic kidney epithelial cells (HEK293) with three plasmid constructs encoding: an expression cassette for normal human RPE65, helper virus-derived sequences, and AAV2 capsid and rep sequences required for packaging of the RPE65 cassette into recombinant AAV2 particles. To generate the DS in cell culture, HEK293 cells from a qualified Master Cell Bank (MCB) are expanded in (b) (4) roller bottles and transfected with the plasmid DNAs. The

(b) (4)

The voretigene neparvovec-rzyl Drug Product (DP) is manufactured at (b) (4), with (b) (4) sterile filtration and filling into plastic ((b) (4)) vials, and stored at not greater than -65°C. There is no change in formulation or dilution from DS to DP.

The Diluent is also manufactured at (b) (4). The manufacturing process for Diluent includes (1) preparation of a diluent compounding solution using (b) (4) P188 (b) (4), sodium chloride, (b) (4), and water for injection (WFI) (2) (b) (4) and (3) sterile filtration into (b) (4) vials. The Diluent is stored at not greater than -65°C.

Manufacturing Controls and Control Strategy

Manufacturing process consistency is controlled by (1) raw material and reagent qualification programs, (2) in-process monitoring and in-process control testing, (3) validation of the manufacturing process, and (4) lot release tests. The raw material qualification program consists of the qualification and monitoring of raw material suppliers, control and maintenance of specifications for raw materials and components, and implementation of appropriate sampling plans and tests to determine the acceptability of raw materials and components. A risk assessment was performed on each manufacturing process step to identify process parameters that impact the quality, purity, safety, and potency of the product. Critical process parameters (CPPs) were established based on process characterization and manufacturing risk assessment studies during process development stages. The CPPs define acceptable operating ranges for each manufacturing step necessary to ensure a consistent final product that meets the predefined product quality attributes (lot release specifications).

In-process monitoring ensures that each manufacturing step meets pre-defined process operating parameters and in-process control testing is performed at key manufacturing steps. Lot release testing is performed as the final confirmation of product quality before releasing the product for distribution.

Process Validation

The commercial manufacturing process for voretigene neparvovec-rzyl DS was adapted by Spark Therapeutics, Inc. from a process developed under an Investigational New Drug application originally submitted by The Children's Hospital of Philadelphia (CHOP). Validation of the process for manufacturing voretigene neparvovec-rzyl DS was conducted by manufacturing one Process Performance Qualification (PPQ) DS lot, which consisted of (b) (4) sub-lots, each at a (b) (4)-roller bottle scale, at Spark Therapeutics, Inc. The DS manufacturing process was executed for the (b) (4) sub-lots that comprised the PPQ DS lot. All (b) (4) sub-lots met all pre-defined PPQ acceptance criteria. All the (b) (4) was below the alert and action levels

for all sub-lots. The additional (b) (4) testing conducted pre- and post-hold met the acceptance criteria set in the PPQ protocol.

Process validation for the DP manufacturing process was conducted by manufacturing one PPQ DP lot at commercial scale, at (b) (4). The data demonstrate that the shipping, thawing, filtration, and filling steps of the manufacturing process are controlled effectively at the commercial scale to produce DP that consistently meets the established product quality acceptance criteria.

Process validation for the Diluent manufacturing process was conducted by manufacturing one Diluent PPQ lot, at (b) (4). The data confirmed that the process is consistent and controlled to meet the established Diluent acceptance criteria.

Manufacturing Risks

The risk of product contamination with other Adventitious Viral Agents (AVA) is minimized using well-characterized biological starting materials, such as the HEK293 cell bank. The risk of AVA is also reduced by controlling the raw materials of biological origin (i.e., fetal bovine serum, (b) (4)), controlling the manufacturing process, and testing the cell bank and the DS by *in vitro* and *in vivo* assay methods.

Specifications

The analytical methods and their validations and/or qualifications reviewed for the LUXTURNA DS, DP, and Diluent were found to be adequate for their intended purpose.

The final lot release specifications of DP and Diluent are shown in the tables below.

Table 2. Drug Product Specifications

Assay	Test Site / Method Number	Acceptance Criteria
Physicochemical		
Appearance (Visual Inspection)	Spark / QC028	Clear and colorless solution, free of visible
pH	Spark / QC020	(b) (4)
(b) (4)	Spark / QC019	(b) (4)
Concentration of Pluronic (µg/mL)	(b) (4)	(b) (4)
Extractable Volume (mL)	(b) (4)	(b) (4)
Identity		
Vector Genome Identity by (b) (4)	Spark / QC067	Positive for hRPE65v2
Concentration		

Vector Genome Concentration Assay (vg/mL)	Spark / QC062	(b) (4)
Activity/Potency		
(b) (4)	Spark / QC069	(b) (4)
Gene Product Expression by (b) (4) Assay	Spark / QC033	Positive for hRPE65v2 gene
In Vitro Relative Potency of (b) (4) by (b) (4) Assay (b) (4)	(b) (4)	(b) (4)
In Vitro Relative Potency of (b) (4) Assay	(b) (4)	(b) (4)
Purity		
Purity by (b) (4) Assay (b) (4)	Spark / QC003	(b) (4)
Safety		
Endotoxin (IU/mL)	(b) (4)	(b) (4)
Particulate Matter	(b) (4)	(b) (4)
Sterility	(b) (4)	No Growth

Table 3. Diluent Specifications

Assay	Test Site	Method Number	Acceptance Criteria
Physiochemical			
Appearance (Visual Inspection)	Spark Therapeutics, Inc.	QC028	Clear and colorless solution, free of visible particles
pH	Spark Therapeutics, Inc.	QC020	7.3 (b) (4)
(b) (4)	Spark Therapeutics, Inc.	QC019	(b) (4)
Concentration of Pluronic (µg/mL)	(b) (4)	ATP000719	(b) (4)
Particulate Matter	(b) (4)	(b) (4)	(b) (4)
Extractable Volume (mL)	(b) (4)	(b) (4)	(b) (4)

Safety			
Sterility	(b) (4)	SOP 1140	No growth
Endotoxin (IU/mL)	(b) (4)	(b) (4)	(b) (4)

Impurity profile

Impurities can be classified into product-related and process-related impurities. Product-related impurities are those derived from incomplete packaging of the vector genome (such as empty capsids and non-infectious virus). Process-related impurities may include HEK293 cellular DNA and proteins, plasmid DNA, and reagents used for product manufacturing that are not intended to be present in the final product.

Impurities are reduced by multiple purification procedures during the manufacturing process. The residual levels of product-related impurities (e.g., empty capsids, non-infectious virus) and process-related impurities (e.g., residual host cell DNA, residual plasmid DNA, residual E1A DNA, residual HEK293 protein, (b) (4) , residual bovine albumin, residual (b) (4) , residual Cesium) are all measured to meet the acceptance limits.

Container closure-DP

The DP and Diluent are filled into 2-mL (b) (4) plastic vials ((b) (4), cyclic olefin polymer). The plastic vials are stoppered with a 13 mm (b) (4) grey chlorobutyl stopper ((b) (4) stopper) and sealed with a 13 mm (b) (4) aluminum Flip-Off® design seal. The top surface and flange sides of the stopper are (b) (4) . (b) (4) testing was performed at (b) (4) to evaluate the integrity of the container closure system stored at (b) (4) for stability studies. This test method was validated for the container closure system described above and the results were acceptable. Additionally, this testing will be performed at pre-determined intervals for ongoing stability evaluation. In addition, a (b) (4) test method was validated to evaluate the integrity of the container closure system stored (b) (4) for shipping studies, and the results were acceptable.

One vial of LUXTURNA DP and two vials of Diluent are placed in a plastic tray; the tray with the vials is placed into a labeled paper carton; the carton is heat-sealed in a pouch and shipped to the distributor (b) (4) shipper, and stored in a validated freezer at ≤-65°C.

b) CBER Lot Release

The lot release protocol template for LUXTURNA was submitted to CBER for review and found to be acceptable after revisions. A Laboratory Quality Product Testing Plan was developed by CBER and will be used for routine lot release.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of voretigene neparvovec-rzyl (AAV2-hRPE65v2) are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Table 4. Manufacturing Facilities Table for voretigene neparvovec-rzyl (AAV2-hRPE65v2; LUXTURNA)

Name/Address	FEI number	DUNS number	Inspection/ waiver	Justification /Results
Drug Substance Manufacturing and Testing Spark Therapeutics Inc. 3737 Market St Philadelphia, PA 19104 USA	3011194531	079498241	Pre-License Inspection	CBER August 21-25, 2017 VAI
(b) (4)			Waived	CBER (b) (4) VAI
			Waived	ORA (b) (4) VAI
			Waived	ORA (b) (4) NAI
			Waived	ORA (b) (4) VAI

VAI: Voluntary Action Indicated
NAI: No Action Indicated
ORA: Office of Regulatory Affairs

CBER conducted a pre-license inspection (PLI) of Spark Therapeutics Inc., Philadelphia PA, from August 21 - 25, 2017 for voretigene neparvovec-rzyl DS 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).

CBER had previously inspected the (b) (4) location from (b) (4). All inspectional issues were resolved and the inspection was classified as VAI.

Office of Regulatory Affairs (ORA) conducted a routine surveillance inspection at (b) (4) location from (b) (4). All inspectional issues were resolved and the inspection was classified as VAI.

ORA conducted a surveillance inspection of (b) (4) from (b) (4). No Form FDA 483 was issued for this inspection and the inspection was classified as no action indicated (NAI).

ORA conducted a routine surveillance inspection of (b) (4) from (b) (4). All inspectional issues were resolved and the inspection was classified as VAI.

d) Environmental Assessment

An environmental assessment (EA) was prepared pursuant to 21 CFR part 25. The EA provided a quantitative assessment of LUXTURNA environmental exposure based on data from biodistribution and shedding studies, lot release testing and related nonclinical studies, and a worst case assumption in each case. No significant environmental impacts on the quality of the human environment were identified. A Finding of No Significant Impact (FONSI) memorandum has been prepared.

e) Product Comparability

A comparability evaluation was conducted to demonstrate that the voretigene neparvovec-rzyl product manufactured by Spark Therapeutics, Inc. is comparable to the Phase 3 clinical material manufactured at CHOP. The DS PPQ lot manufactured at Spark Therapeutics, Inc. was compared to the Phase 3 clinical material manufactured at CHOP by comparing the lot release testing data and side-by-side testing. A supplemental comparability evaluation of final filled voretigene neparvovec-rzyl DP to the Phase 3 clinical material was conducted under a separate protocol by side-by-side testing including all the tests for product potency. The lot release data, along with the results from the side-by-side comparability assessment showed that the PPQ Lot manufactured by Spark Therapeutics, Inc. is comparable to the Phase 3 clinical material manufactured at CHOP.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Subretinal delivery (bilateral, simultaneous administration) of AAV2-hRPE65v2 (8.25×10^{10} vg/eye) to RPE65 mutant dogs resulted in improved pupillary responses, ERGs, and visual behavior, and reduced nystagmus. RPE65 protein was detected in the RPE cells located in the portion of the retina exposed to the vector. Subretinal delivery (bilateral, sequential, with one eye injected at Day 0 and the contralateral eye injected 13-15 days later) of AAV2-hRPE65v2 (1.5×10^{11} vg/eye) resulted in improved navigation and pupillary responses within 2 weeks post-first eye injection. Further improvement in visual behavior and diminution in nystagmus was observed post-second eye injection.

Single-dose and repeat-dose toxicology studies were conducted in normal-sighted dogs, RPE65 mutant dogs, and normal-sighted non-human primates (NHPs). Dosing regimens for the single-dose studies consisted of: 1) unilateral administration, or 2) bilateral, simultaneous administration. Several subretinal dosing regimens were employed for the repeat-dose studies. The clinically relevant schedule consisted of injection of AAV2-hRPE65v2 into one eye, followed (at an interval of at least 2 weeks) by injection into the contralateral eye (bilateral, sequential

administration). Additional dosing regimens included: 1) administration to one eye, followed (at an interval of 98 days) by administration to the contralateral eye, with subsequent re-administration to one eye (bilateral, sequential/re-administration), and 2) administration to both eyes, followed (at an interval of approximately 30 days) by re-administration to one eye (bilateral, simultaneous/re-administration; ipsilateral).

Following single or repeat subretinal administration of AAV2-hRPE65v2 in dogs and NHPs, no toxicity was observed in non-ocular tissues. Occasional inflammation in the retina, attributed to the surgical delivery procedure, was detected. Subretinal injection of 1.5 x 10^{12} vg/eye of a precursor AAV2-hRPE65v2 vector product in normal-sighted dogs resulted in ocular inflammation and retinal degeneration observed microscopically in regions exposed to the vector. This dose level is 10-fold higher than the clinical dose level of 1.5 x 10^{11} vg/eye in the applicant's 'Dosage and Indication' section of the label. The no-observed-adverse-effect-level (NOAEL) in NHPs was 7.5 x 10^{11} vg/eye, which is 5-fold higher than the proposed clinical dose level specified in the Dosage and Administration' section of the Prescribing Information.

The biodistribution (BD) profile of AAV2-hRPE65v2 in normal-sighted nonhuman primates and a precursor AAV2-hRPE65v2 vector product in normal-sighted dogs was determined out to 3 months following subretinal administration. The highest levels of vector DNA were detected primarily in the intraocular fluids (anterior chamber fluid and vitreous) of vector-injected eyes. Low levels of the vector DNA sequence were detected in the optic nerve of the vector-injected eye. There was very limited BD of low levels of vector DNA to non-ocular tissues (e.g., spleen and liver). No vector DNA was detected in the gonads.

There was no evidence of a pro-inflammatory T cell response to the RPE65 protein in the NHPs. There were no pro-inflammatory T cell responses to the AAV2 capsid, except for one NHP previously exposed to an AAV2 vector that developed a CD4+ T cell response. There were no pro-inflammatory T cell responses to the AAV2 capsid in any dog, and a limited T cell response to human RPE65 was observed in RPE65 mutant dogs.

Antibodies to human RPE65 were detected transiently in isolated cases in dogs and NHPs. Antibodies to the AAV2 capsid were present in the anterior chamber fluid and/or serum of normal-sighted and RPE65 mutant dogs. Antibodies to the AAV2 capsid were not detected in naïve NHPs, but were detected in NHPs previously exposed to AAV2 vector.

Based on the biological attributes of AAV2-hRPE65v2, the current scientific publications, and the applicant's pharmacology and toxicology data, studies to evaluate safety pharmacology, developmental and reproductive toxicity, genotoxicity, and carcinogenicity/tumorigenicity were not conducted or required for AAV2-hRPE65v2.

5. CLINICAL PHARMACOLOGY

LUXTURNA vector shedding and biodistribution were investigated in a study measuring LUXTURNA DNA in tears from both eyes, and from serum, and whole blood of patients in the Phase 3 study. In summary, LUXTURNA vector was shed transiently and at low levels in tears from the injected eye in 45% of the patients in the Phase 3 study, and occasionally (7%) from the uninjected eye until Day 3 post-injection.

In 29 patients who received bilateral administrations, LUXTURNA vector DNA was present in tear samples of 13 patients (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 patients (8 of 13). Three patients (10%) had vector DNA in tear samples until Day 3 post-injection, and two patients (7%) had vector DNA in tear samples for around two weeks post-injection. In another two patients (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%) patients, including two with vector DNA in tear samples up to Day 3 following each injection.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

A Phase 1 study and a Phase 3 study form the basis of the review team's recommendation for regular approval of LUXTURNA for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. The Phase 3 study provides the primary evidence of effectiveness. Both the Phase 1 and Phase 3 studies contribute to the safety database.

Study Description

The Phase 1 study was an open-label, dose-escalation safety study in a total of 12 patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Eleven of the 12 patients received subretinal injection of LUXTURNA to each eye with an injection interval ranging from 1.7 to 4.6 years. One patient received subretinal injection in only one eye. Three doses were evaluated in the Phase 1 study. There was no clear dose effect for safety, bioactivity, or preliminary efficacy. The high dose (1.5×10^{11} vector genome in an injection volume of 0.3 mL) was chosen for the Phase 3 study.

The Phase 3 study was an open-label, randomized, controlled, cross-over trial. It was designed to evaluate efficacy and safety of sequential subretinal injection of LUXTURNA to each eye. Patients were randomized in a 2:1 ratio to either the LUXTURNA treatment group or the observational control group, and were followed for one year for the primary efficacy assessment. Patients in the control group were crossed over to receive LUXTURNA after one year of observation.

All the patients treated in Phase 1 and Phase 3 studies received a short course of oral corticosteroid to suppress potential immune reactions to the vector capsid and RPE 65 protein.

Efficacy Endpoints

The primary efficacy endpoint in the Phase 3 study was change in multi-luminance mobility testing (MLMT) performance from Baseline to one year after LUXTURNA administration. MLMT was designed to measure functional vision, as assessed by the ability of a patient to navigate a course accurately and at a reasonable pace at different levels of environmental illumination. The MLMT was assessed using both eyes and each eye separately at one or more of seven light levels, ranging from 400 lux (corresponding to a brightly lit office) to 1 lux (corresponding to a moonless summer night). Each light level was assigned a score code ranging from 0 to 6. A higher score indicated that a patient was able to pass the MLMT at a lower light level. A score of -1 was assigned to patients who could not pass MLMT at a light level of 400 lux. The MLMT of each patient was videotaped and assessed by independent, blinded graders. The MLMT score was determined by the lowest light level at which the patient was able to pass the MLMT. The MLMT score change was defined as the difference between the score at Baseline and the score at a follow-up visit. A positive MLMT score change indicated improvement in the

MLMT performance. The primary efficacy analyses were assessed at Year 1 in the intention-to-treat (ITT) population, defined as all randomized patients.

Additional efficacy endpoints included full-field light sensitivity threshold (FST) and visual acuity (VA).

Clinical Efficacy Findings

The Phase 3 study enrolled 31 patients from two sites in the United States. Of the 31 enrolled patients, 21 patients were randomized to the treatment group with discontinuation of one patient at the baseline visit. Ten patients were randomized to the control group with withdrawal of consent of one patient at the screening visit. The nine patients in the control group were crossed over to receive LUXTURNA after one year of observation. The average age of the 31 randomized patients was 15 years (ranging from 4 to 44 years), including 20 (64%) pediatric patients age ranging from 4 to 17 years and 11 adult patients. The subretinal injection interval between the two eyes of each patient ranged between 6 and 18 days.

Primary efficacy endpoint

Table 5 summarizes the primary efficacy endpoint results, the median MLMT score change from Baseline to Year 1 in the LUXTURNA treatment group as compared to the control group. A median MLMT score change of two (2) was observed in the LUXTURNA treatment group, while a median MLMT score change of zero (0) was observed in the control group, when using both eyes or the first-treated eye. An MLMT score change of two or greater is considered a clinically meaningful benefit for functional vision.

Table 5. Efficacy Results of the Phase 3 Study at Year 1, Compared to Baseline

Efficacy Outcomes	LUXTURNA n=21	Control n=10	Difference (LUXTURNA minus Control)	p-value
MLMT score change using both eyes, median (min, max)	2 (0, 4)	0 (-1, 2)	2	0.001
MLMT score change using the first-treated eye, median (min, max)	2 (0, 4)	0 (-1, 1)	2	0.003

Source: FDA Statistical and Clinical Reviews

Table 6 and Table 7 show the number and percentage of patients with different magnitudes of MLMT score change using both eyes and individual eyes, respectively, at Year 1. Using both eyes, eleven patients (11/21, 52%) in the LUXTURNA treatment group had an MLMT score change of two or greater, while only one patient (1/10, 10%) in the control group had an MLMT score change of two (Table 6). Using the first-treated eye and second-treated eye separately, fifteen patients (15/21, 71%) in the LUXTURNA treatment group had an MLMT score change of two or greater, while no patient in the control group had a score change of 2 or greater (Table 7).

Table 6. Magnitude of MLMT Score Change Using Both Eyes at Year 1

MLMT Score Change	LUXTURNA 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 and Clinical Reviews

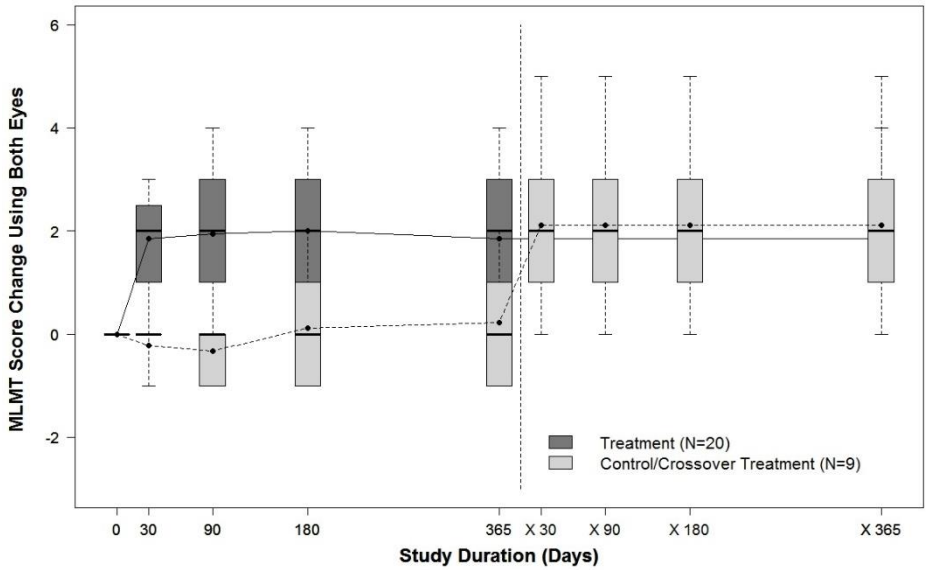
Table 7. Magnitude of MLMT Score Change Using Individual Eyes at Year 1 (ITT)

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 and Clinical Reviews

Figure 1 shows the effect of LUXTURNA over the two-year follow-up period in the LUXTURNA treatment group, as well as the effect of LUXTURNA in the control group after crossing over to receive LUXTURNA at Year 1. A median MLMT score change of two was observed for the LUXTURNA treatment group at Day 30 after LUXTURNA administration, and this effect was sustained over the remaining follow-up visits throughout the two-year period. For the control group, a median MLMT score change of zero (0) was observed at all four follow-up visits during the first year; however, after crossing-over to receive LUXTURNA, the patients in the control group showed a similar response to LUXTURNA as compared to the patients in the LUXTURNA treatment group.

Figure 1. 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 each 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 cross-over at Year 1 to receive LUXTURNA.
Source: FDA Statistical and Clinical Reviews

Additional efficacy endpoints

Analysis of white light FST testing showed statistically significant improvement from Baseline to Year 1 in the LUXTURNA treatment group compared to the control group. The change in visual acuity from Baseline to Year 1 was not significantly different between the LUXTURNA treatment and control groups. However, exploratory analysis of visual acuity showed a trend towards improvement in the LUXTURNA treatment group.

Efficacy Conclusion

The submitted data provide sufficient evidence of effectiveness for patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. This conclusion is based on improvement in functional vision, as determined by a significant difference in MLMT score change from Baseline to Year 1 between the LUXTURNA treatment and control groups, when using either both eyes or the first-treated eyes, in 31 patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy in the Phase 3 study. This benefit is clinically meaningful.

Bioresearch Monitoring

Bioresearch Monitoring (BIMO) inspections were conducted at two clinical sites that participated in the conduct of Study AAV2-hRPE65v2-301. The inspections did not reveal any issues that impact the data submitted in this application.

b) Pediatrics

Pediatric Research Equity Act (PREA) is not applicable to LUXTURNA for the treatment of biallelic *RPE65* mutation-associated retinal dystrophy because LUXTURNA was granted orphan drug designation for the indication.

Of the 41 patients enrolled in Phase 1 and Phase 3 studies, there were 25 pediatric patients, 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 age subgroups or in comparison to the adults in the trial.

c) Other Special Populations

None.

7. SAFETY

The safety population included a total of 41 patients (81 eyes) who received subretinal administration of LUXTURNA (12 patients from Phase 1 and 29 patients from Phase 3). Twenty-seven (27/41, 66%) patients had ocular adverse reactions that involved 46 injected eyes (46/81, 57%). The most common adverse reactions (incidence ≥ 5%) were conjunctival hyperemia, cataracts, increased intraocular pressure, retinal tears, dellen (thinning of corneal stroma), macular hole, eye inflammation, macular breaks, subretinal deposits, eye irritation, eye pain, and maculopathies (wrinkling on the surface of the macula) (Table 8). These ocular adverse reactions may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products. Most of these ocular adverse reactions were temporary and responded to medical management.

There were no deaths in the clinical studies. There were two serious ocular adverse reactions, including (1) endophthalmitis (infection inside of the eye) with a series of subsequent complications as a result of the infection and the treatment, and (2) loss of vision due to fovea thinning as a result of the subretinal injection.

Systemic adverse events included hyperglycemia, nausea, vomiting, and leukocytosis. These systemic events were likely caused by systemic corticosteroid use and reactions to anesthesia.

Table 8. Ocular Adverse Reactions Following Treatment with LUXTURNA (N=41)

Adverse Reactions	Patients 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 (infection inside of the eye)	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%)

Note: *Transient appearance of a ring-like deposit at the retinal injection site 1-6 days after injection without symptoms.
Source: Modified from the applicant's BLA submission

At all doses evaluated in the Phase 1 and Phase 3 studies, immune reactions and extra-ocular exposure have been mild, even with sequential administration to each eye. There were no clinically significant cytotoxic T-cell responses to either the AAV2 vector capsid or the transgene product *RPE65* in any of the patients. 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.

In summary, the more serious risks associated with subretinal administration of LUXTURNA include endophthalmitis, permanent decline in visual acuity, increased intraocular pressure, retinal abnormalities (e.g., retinal tears or breaks), and cataract development and/or progression. These risks can be mitigated by routine medical management, appropriate labeling of Prescribing Information (PI), and the postmarketing plan proposed by the applicant. In the setting of concomitant use of oral corticosteroid at the time of subretinal injection of LUXTURNA, the immune response to AAV capsid and RPE65 was mild.

Postmarketing Pharmacovigilance

The applicant will continue collecting safety and efficacy information for the 41 patients who participated in Phase 1 and Phase 3 studies and are currently enrolled in the ongoing 15-year long-term follow-up (LTFU) study under IND 13408. The ongoing LTFU study includes annual office visits to assess both safety and efficacy for the first five years, followed by annual phone contact or office visit for the subsequent 10 years. In addition, the applicant proposed the following postmarketing measures:

(1) adequate Prescribing Information;

(2) distribution and use of LUXTURNA through Centers of Excellence, and mitigating risks by training pharmacists and surgical staff;

(3) a prospective multi-center observational registry to collect safety information for patients treated with LUXTURNA. The study will enroll at least 40 patients for at least a 5-year period of enrollment.

The pharmacovigilance and clinical review team recommended that the applicant revise the voluntary registry study to include ophthalmological examinations to collect more data on safety. Based on review of available data, and input from FDA's Center for Drugs Evaluation and Research (CDER) and the Cellular, Tissue, and Gene Therapies Advisory Committee (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 practice, adequate Prescribing Information as well as the voluntary postmarketing plans proposed by the applicant. The reviewed safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategies (REMS), a safety postmarketing requirement (PMR) study, or a safety postmarketing commitment (PMC) study.

8. ADVISORY COMMITTEE MEETING

A meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) was held on October 12, 2017 to provide feedback to FDA regarding clinical efficacy and safety, and an overall benefit-risk assessment of LUXTURNA.

Summary of discussion:

- A 2-light level improvement in MLMT (i.e., an MLMT score change of 2) is clinically meaningful.

- The potential risks associated with subretinal injection of LUXTURNA and concomitant corticosteroid use are acceptable for the pediatric population, even in the very young population.

- The retinal cellular proliferation is not complete until 8 to 12 months of age, and LUXTURNA may be diluted or lost during the cellular proliferation process.

- Further study may be needed to support repeat administration of previously treated eyes if the efficacy of LUXTURNA declines over time.

- The Committee voted 16 (Yes) to 0 (No) to the question, "Considering the efficacy and safety information provided in the briefing document, as well as the presentations and discussions during the AC meeting**,** does voretigene neparvovec-rzyl have an overall favorable benefit-risk profile for the treatment of patients with vision loss due to confirmed biallelic *RPE65* mutation-associated retinal dystrophy?"

9. OTHER RELEVANT REGULATORY ISSUES

Not applicable

10. LABELING

The proposed proprietary name, LUXTURNA, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on June 19, 2017, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on August 10, 2017.

The APLB found the prescribing information (PI) and carton/container labels to be acceptable from a promotional and comprehension perspective. The review committee negotiated revisions to the PI, including the INDICATIONS statement. All issues were acceptably resolved after exchange of information and discussions with the applicant.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

Based on the magnitude and durability of the treatment effect demonstrated in the Phase 3 study, and the unmet medical need, the review team recommends regular approval for LUXTURNA.

b) Risk/ Benefit Assessment

Efficacy of LUXTURNA 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 major risks associated with subretinal administration of LUXTURNA and concomitant oral corticosteroid use include endophthalmitis, permanent vision loss, increased intraocular pressure, retinal tears or breaks, and cataract development and/or progression, which might have long-term consequences, especially if they were left untreated. However, these risks can be mitigated by management within routine medical practice, 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. The review team recommends regular approval of LUXTURNA 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.

c) Recommendation for Postmarketing Activities

The review committee agrees with the pharmacovigilance activities in the applicant's proposed pharmacovigilance plan. The pharmacovigilance plan includes a long-term follow-up study of the clinical trial patients, a voluntary patient registry, and routine pharmacovigilance for adverse event reporting.

The applicant and the FDA reached agreements on the following CMC Postmarketing Commitments (PMC):

(1) Spark Therapeutics, Inc. commits to provide the shipping validation study protocol for shipment of the Drug Product from the distributor to a clinical site (or to Spark Therapeutics, Inc.) by January 31, 2018. A final study report will be submitted as a "Postmarketing Commitment - Final Study Report" by June 30, 2018.

(2) Spark Therapeutics, Inc. commits to complete the verification studies for the following assays:
    a. (b) (4)
    b. (b) (4) tests for particulate matter for the Drug Product and Diluent, performed by (b) (4).

A final study report will be submitted as a "Postmarketing Commitment - Final Study Report" by March 31, 2018.

(3) Spark Therapeutics, Inc. commits to perform 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) following approval, and evaluate if the acceptance criteria for LUXTURNA lot release tests (including the (b) (4)) continue to provide adequate quality control for DS and DP based on the new data obtained from those tests. A final study report will be submitted as a "Postmarketing Commitment - Final Study Report" by March 31, 2020.

(4) Spark Therapeutics, Inc. commits to conduct stability studies on the HEK293 Master Cell Bank (MCB) used for Drug Substance manufacture. (b) (4), "Postmarketing Commitment - Final Study Report" by March 31, 2018.

(5) Spark Therapeutics, Inc. commits to qualify the (b) (4). A final study report will be submitted as a "Postmarketing Commitment - Final Study Report" by March 31, 2018.

(6) Spark Therapeutics, Inc. commits to revise procedures for visual inspection to incorporate statistically sound sampling plans (e.g., AQL) following the 100% inspection. The sampling plan will include appropriate acceptance criteria for critical and major defects. A final study report will be submitted as a "Postmarketing Commitment - Final Study Report" by June 30, 2018 to include the procedure and the results of the revised visual inspection process for the next product lot manufactured.

(7) Spark Therapeutics, Inc. commits to perform (b) (4) as cleaning verification. A final study report will be submitted as a "Postmarketing Commitment - Final Study Report" by September 30, 2018 to include the revised procedure for performing cleaning verification and the results of testing for the next lot manufactured.