

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research
Division of Epidemiology**

Pharmacovigilance Original BLA Memorandum

From: Bethany Baer, MD
Medical Officer, Pharmacovigilance Branch (PVB),
Division of Epidemiology (DE),
Office of Biostatistics and Epidemiology, CBER

To: Lilia Bi
BLA Chair
Office of Tissues and Advanced Therapies

Through: Adamma Mba-Jonas, MD
Acting Branch Chief, PVB, OBE, CBER

Scott Proestel, MD
Director, Division of Epidemiology, OBE, CBER

Subject: Review of Pharmacovigilance Plan

Applicant: Spark Therapeutics, Inc.

Product: Luxturna (Voretigene neparvovec [AAV2-hRPE65v2])

Application Number: BLA 125610/o

Proposed Indication: Gene therapy for treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy

Submission Date: May 16, 2017

Action Due Date: Jan. 12, 2018

1. Objective

The purpose of this review is to assess the adequacy of the pharmacovigilance plan based on the safety profile of Luxturna (Voretigene neparvovec [AAV2-hRPE65v2]).

2. Product Information

• Product description

Luxturna is a gene therapy product that uses the adeno-associated virus 2 (AAV2) vector to deliver the 65 kiloDalton retinal pigment epithelium protein (RPE65) to the retina by a one time, direct subretinal injection. Its proposed use is to treat patients who have biallelic RPE65 mutation-associated retinal dystrophy, which includes a subset of patients clinically diagnosed with Leber amaurosis and retinitis pigmentosa.

• Proposed dosing regimen and formulation

Luxturna is available as a concentrate for solution for a one time subretinal injection. The product requires a 1:10 dilution prior to use, and 0.3 mL volume containing 1.5×10^{11} vector genomes is injected per eye. A patient is treated with a single administration to one eye followed by a single administration to the other eye on separate days 12 days (+/- 6 days) apart.

3. Pertinent Regulatory History

- Luxturna was granted Orphan Drug Designation for treatment of Leber congenital amaurosis due to RPE65 mutation on Jun. 24, 2008.
- Luxturna was granted Breakthrough Therapy Designation for treatment of Leber congenital amaurosis due to RPE65 mutation on Sep. 24, 2014.
- Luxturna was granted Orphan Drug Designation for the treatment of inherited retinal dystrophy due to biallelic RPE65 mutations on Nov. 29, 2016.
- Luxturna is currently not marketed in any country.
- On Oct. 12, 2017, the Cellular, Tissue, and Gene Therapies Advisory Committee discussed Luxturna. The committee voted 16:0 in support of Luxturna's overall favorable benefit-risk profile for the treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy.

4. Materials Reviewed

Materials reviewed in support of this assessment include:

- Applicant's Risk Management Plan (RMP), version 1.0 (Module 1.16 of 125610/0)
- Applicant's Summary of Clinical Safety (Module 2.7.4 of 125610/0)
- Applicant's Annotated Prescribing information (Module 1.14 of 125610/0)
- Applicant's Protocol: A Prospective, Multicenter, Observational Safety registry for Subjects Treated with Voretigene Neparvovec, Draft Version, dated Feb. 3, 2017. (Module 1.16 of 125610/0)
- OTAT clinical reviewer Advisory Committee briefing document
- Applicant response to FDA Information Request, (email response dated Nov. 9, 2017)

5. Clinical Safety Database

The clinical program for Luxturna consisted of 3 clinical trials.

Study	No. of subjects	Description	Age range
AAV-hRPE65v2-101 Phase 1 dose escalation	12	Single unilateral injection at one of 3 dose levels	8-44 years

Study	No. of subjects	Description	Age range
AAV-hRPE65v2-102 Phase 1 follow-on	11 (all 11 from study 101)	Contralateral eye injection after study 101. High dose from Study 101 used.	11-46 years
AAV-hRPE65v2-301 Phase 3	29 total subjects received injection (initially 21 in intervention group and 10 in control group)	Open-label, randomized. Ten control subjects crossed over to intervention group after 1 year of observation.	4-44 years
Total	41 subjects		4-46 years

The race of the subjects in the clinical program was: 76% White, 12% Asian, 7% American Indian or Alaska Native, and 5% Black or African American.

All 41 subjects in the clinical program experienced at least one treatment-emergent adverse event (TEAE). The most common TEAEs were: headache (21/41, 51%), leukocytosis (17/41, 41%), pyrexia (17/41, 41%), nasopharyngitis (15/41, 37%), nausea (14/41, 34%), cough (13/41, 32%), and vomiting (13/41, 32%). The most frequent ocular TEAEs were conjunctival hyperemia (9/41, 22%), intraocular pressure increased (8/41, 20%), and cataract (7/41, 17%). Most ocular TEAEs were associated with the administration procedure and resolved without sequelae. There were ocular TEAEs that required intervention (e.g., cataract, retinal tears).

There were 8 serious TEAEs in 7 subjects. Two of these serious adverse events (SAEs) were determined by the applicant to be related to Luxturna's clinical program, including product administration and follow-up care. The first case was a 19-year-old female in study 301 who was treated with Luxturna following a year in the control group. It was noted that there was a raised bleb affecting the fovea in both eyes following the subretinal injection of Luxturna. The patient developed decreased central vision post-operatively and was found to have foveal thinning in both eyes. There was no improvement in the central vision at 1 year follow-up and the patient had permanent loss of foveal function in the right eye (baseline 20/150 decreased to 20/320 after Luxturna). The applicant considered this event to be related to Luxturna's administration procedure.

The second SAE related to the procedure and follow-up treatment was a 21-year-old male who had increased intraocular pressure following Luxturna injection in his second eye. He developed endophthalmitis (vitreal culture positive for *Staphylococcus epidermidis*) at 4 weeks post-injection. He was treated with antibiotics and depo-steroids. The infection resolved, but the patient had continued increased intraocular pressure in the eye. The increased intraocular pressure was felt to be due to the depo-steroid injection. He underwent a trabeculectomy with improvement, but he continued to have maculopathy and optic atrophy. The applicant considered this event to be related to the treatment for endophthalmitis rather than directly related to the procedure.

Reviewer Comment: The Division of Epidemiology (DE) agrees with the applicant that these two SAEs were related to the Luxturna clinical program. DE notes that the treatment for endophthalmitis was necessary due to a complication of Luxturna's administration procedure.

The other six serious TEAEs which were determined by the applicant to be unrelated to Luxturna's clinical program were: 2 separate seizure episodes in a patient with a history of a

seizure disorder (8 months after Luxturna), a reaction to anesthesia given for oral surgery (11 months after Luxturna), anal fistula in a patient with a history of Crohn's disease (3 years after Luxturna), planned orchidopexy for cryptorchism (2 years after Luxturna), and paresthesias (5 years after Luxturna).

Reviewer Comment: Due to the underlying conditions seen in these patients and the long time period since Luxturna receipt, DE agrees that these six TEAEs are unrelated to Luxturna or the administration of Luxturna.

There were three non-serious adverse events which the applicant classified as related to Luxturna. The three patients all received the same lot of Luxturna, which was given to 7 patients total. These three patients developed retinal deposits (also called a subretinal precipitate) that were asymptomatic and resolved spontaneously without sequela.

6. Summary of Prior Marketed Experience

Not applicable. The product has not been previously approved or used outside of the clinical trials. It is a first-in-class product.

7. Applicant's Pharmacovigilance Plan

In addition to routine pharmacovigilance, the applicant is proposing two studies for the postmarketing period:

Study name	Description	Milestone dates
AAV2-hRPE65v2-LTFU-01	Long-term follow-up (LTFU) study for participants in the clinical trials	Annual updates Last patient visit in 2030
Patient Safety Registry	Prospective, multi-center, observational registry of patients treated with Luxturna at approved centers	To be determined

Study AAV2-hRPE65v2-LTFU-01 will follow the 41 patients who have received Luxturna in the clinical program. It will include an annual history, physical and ophthalmic examinations (including fundus photography and optical coherence tomography (OCT)), blood tests, urinalysis, and retinal/visual function tests. The follow-up study will monitor the development or exacerbation of oncologic, hematologic, neurologic, auto-immune diseases, as well as any other adverse events that are possibly related to Luxturna or the administration procedure. The follow-up time for this study is 15 years.

The patient safety registry will follow patients for five years post subretinal administration of Luxturna and will collect adverse events related to the important risks and late-occurring adverse events including:

- Development or exacerbation of oncologic, hematologic, neurologic, and auto-immune diseases
- Adverse events that are assessed to be at least possibly related to Luxturna or the administration procedure, increased intraocular pressure, retinal tear, retinal disorder, macular hole, maculopathy, cataract progression or formation, and eye inflammation and infection
- Pregnancy outcomes in Luxturna patients and female partners of patients

The variables that are collected in this non-interventional registry will be determined based on the treating physician's standard of care. The patient will receive a card to show to providers to

facilitate reporting of adverse events. Additionally, the subjects in the registry would be contacted at least annually to solicit reports of adverse events or occurrences of pregnancy. The study variables will be summarized by descriptive statistics or frequency counts. Interim data assessments will occur at least annually. The enrollment will take place at the administering centers and the enrollment period is planned to be 5 years from the first marketing approval date. The Division of Epidemiology (DE) provided comments to the applicant regarding the registry protocol. The applicant has agreed that the registry will continue until a minimum of 40 patients is enrolled and at least a 5-year period of enrollment has elapsed. Also, the protocol will be modified to include a requirement for an annual ophthalmological exam to ensure identification of any adverse events.

The applicant's pharmacovigilance plan is outlined in Tables 1 and 2 below.

Table 1: Applicant's Pharmacovigilance Plan

Type of Concern	Safety Concern	Planned pharmacovigilance activity
Identified	Increased intraocular pressure	<ul style="list-style-type: none"> • Routine pharmacovigilance • Patient safety registry • LTFU study of clinical cohort
Identified	Retinal tear	<ul style="list-style-type: none"> • Routine pharmacovigilance • Patient safety registry • LTFU study of clinical cohort
Identified	Macular disorders	<ul style="list-style-type: none"> • Routine pharmacovigilance • Patient safety registry • LTFU study of clinical cohort
Identified	Cataract	<ul style="list-style-type: none"> • Routine pharmacovigilance • Patient safety registry • LTFU study of clinical cohort
Identified	Intraocular inflammation/infection	<ul style="list-style-type: none"> • Routine pharmacovigilance • Patient safety registry • LTFU study of clinical cohort
Potential	Retinal detachment	<ul style="list-style-type: none"> • Routine pharmacovigilance • Patient safety registry • LTFU study of clinical cohort
Potential	Tumorigenicity	<ul style="list-style-type: none"> • Routine pharmacovigilance • Patient safety registry • LTFU study of clinical cohort
Potential	Host immune response	<ul style="list-style-type: none"> • Routine pharmacovigilance • Patient safety registry • LTFU study of clinical cohort
Potential	Third party transmission	<ul style="list-style-type: none"> • Routine pharmacovigilance

Table 2: Applicant's Pharmacovigilance Plan for Areas of Missing Information

Area of Missing Information	Planned pharmacovigilance activity
Long term efficacy (>3 years)	<ul style="list-style-type: none"> • Routine pharmacovigilance • LTFU study of clinical cohort
Use in pregnancy and lactation	<ul style="list-style-type: none"> • Routine pharmacovigilance • Patient safety registry
Use in children <3 years of age	<ul style="list-style-type: none"> • Routine pharmacovigilance • Patient safety registry
Long-term safety (>8 years)	<ul style="list-style-type: none"> • Routine pharmacovigilance • Patient safety registry • LTFU study of clinical cohort

As a method to minimize the associated risks with this product and the procedure to administer it, the applicant has proposed limiting distribution to approved centers, which the applicant refers to as “Centers of Excellence” (COEs). The staff at these centers will receive training on the preparation and use of the product. The applicant states that “it is essential that only experienced surgeons are involved in the administration of product to ensure that risks related to the surgical procedure are minimised.”¹ The Risk Management Plan states that the center’s surgical staff would be composed of a lead surgeon and assistant surgeon. The lead surgeon would need to be a board-certified ophthalmologist and a fellowship trained vitreoretinal surgeon with appropriate surgical and clinical experience. The center would also have to be associated with an active ophthalmology practice that has expertise in inherited retinal dystrophies to provide diagnostic confirmation, preoperative evaluation, and post-operative care. Additionally, the center pharmacy would undergo training.

8. Analysis of Applicant's Pharmacovigilance Plan

The applicant has outlined the important identified and potential risks as well as the areas of missing information in the safety specifications of Luxturna’s submitted pharmacovigilance plan. The applicant has proposed labeling which provides information on the risks and techniques and warning signs to minimize the risks. Additionally, the applicant has proposed the actions outlined in section 7.

Safety Issues identified in the Pharmacovigilance Plan:

- Increased Intraocular Pressure: 8 of 41 (20%) subjects in the clinical trials had increased intraocular pressure (IOP). All of the related events were considered non-serious by the study investigators. One serious case was in the subject described above who had endophthalmitis treated with depo-steroid injections. The subsequent increased IOP was considered to be due to the steroid injections.
- Retinal Tear: 4 of 41 (10%) subjects in the clinical program had a retinal tear. All events were repaired by the surgeon during the vector administration procedure and were considered non-serious by the investigators. The retinal tears were all considered related to the administration procedure. Retinal tears are a known complication of vitrectomies and of subretinal injections.
- Macular Disorders: 7 of 41 (17%) subjects in the clinical program had a macular disorder event. Three of these were macular holes, one was foveal dehiscence, and two were maculopathies. The one remaining subject had foveal thinning in one eye and loss of foveal function on the other eye (described in section 5 above). All of these events were considered related to the procedure but not related to the product.

¹ Risk Management Plan, v. 1.0, p. 86.

- Cataract: 7 of 41 (17%) subjects in the clinical program developed or had progression of a cataract during the study period. It is noted that the background rate of cataracts is relatively high for patients with retinal disorders and those who have undergone vitrectomy or other ophthalmic surgical procedures. Therefore, the cataract development could be related to the underlying condition but was potentially exacerbated by the treatment with Luxturna.
- Intraocular inflammation and/or infection related to the procedure: 3 of 41 (7%) subjects in the clinical program had eye inflammation. One case was endophthalmitis (described in section 5 above). All of the events were considered by the investigators to be related to the procedure but not the product.
- Retinal detachment: No cases of retinal detachment were seen in the clinical trials. Retinal detachment has been seen after vitrectomy surgery in other studies and can be caused by a retinal tear.
- Tumorigenicity: No cases of tumor development have been seen in the clinical program. This risk is due to the potential for mutagenesis when a gene therapy is incorporated into the host cell's genome. This product's vector does not contain the *rep* or *cap* genes, so it is not able to replicate independently. Additionally, the DNA appears to remain as a plasmid and does not integrate into the cellular DNA. It is, therefore, felt to be relatively low risk for tumorigenicity.
- Host Immune Response: No cases of clinically significant cytotoxic T-cell response to the vector capsid (AAV2) or the transgene product (RPE65) were seen. There was mild, transient redness and inflammation of the eye in some cases, which can occur with any ocular procedure. The use of topical and oral steroids as well as the planned interval of 6-18 days between administration to the eyes were used in an effort to prevent adverse events due to the host immune response.
- Third Party Transmission: No cases were seen of transmission to a third party such as a healthcare worker or family members of the patients. There were 13/29 (45%) of subjects receiving bilateral administration who had Luxturna vector DNA sequences detected in their tear samples. Most of these reverted to negative after 1 day post-injection. Four of the subjects continued to be positive after 1 day post-injection, and 1 was positive after 14 days post-injection. There were 3/29 (10%) who had Luxturna vector DNA sequences detected in their serum. All were negative at three days post-injection.

One potential safety issue that is not addressed in the applicant's PVP is the occurrence of retinal deposits in 3 patients who received the same lot of the product in the clinical trial. The deposits resolved, and there was no clinical correlation with their presence. With only two lots of product used in all of the clinical trials, the occurrence of the deposits in 3 of 7 patients receiving the second lot suggests that there could be variability between the lots that led to the deposits. This issue was discussed with the ophthalmology consult (Dr. W. Chambers) from CDER. Since no clinical adverse event was seen with these deposits and they self-resolved, it was determined that they are not considered a safety issue. The review team discussed that mention of the retinal deposits should appear in the product label so that administering clinicians and follow-up ophthalmologists would be aware that they were seen. They did not require treatment in the clinical trial, but due to small numbers, only limited data are available.

Reviewer Comment on Areas of Missing Information: The applicant included the patient safety registry as a pharmacovigilance activity to address the area of missing information entitled "long-term safety (>8 years)." Since the registry is only planning to follow patients for 5 years, it will not be providing safety information for >8 years after product administration. DE has discussed this issue with the applicant. The applicant has agreed to modify this table so that the patient safety registry is not included as a method to address long-term safety (>8 years). It

is reasonable to note that the patient safety registry will provide additional data on long-term safety up to 5 years.

The review team determined that a postmarketing requirement (PMR) study is not needed for this product. The risks seen in the clinical trial are expected with the manipulation of the eye due to the administration of the product. The applicant is voluntarily conducting a 15-year follow-up study of the clinical trial patients and is also planning a registry with a 5-year follow-up on patients who receive it in the postmarket setting. As the AAV2 vector used for this product does not contain the *cap* or *rep* genes and does not integrate into the cellular DNA, the risk of tumorigenicity is lower than with other gene therapy products. Five-year follow-up is considered acceptable for this class of vectors.

The review team also determined that a Risk Evaluation and Mitigation Strategy (REMS) is not required for this product. After discussion with the ophthalmology consult, the review team determined that the administration of the product is considered within the scope of a fellowship-trained retina specialist. The applicant has proposed a plan for distributing Luxturna only through specially trained centers. This plan can be conducted on a voluntary basis by the applicant.

9. Recommended Pharmacovigilance Actions

- DE recommends that the applicant modify the Risk Management Plan regarding areas of missing information to reflect that the patient safety registry will provide additional safety information only up to 5 years after treatment. The applicant has agreed to make this modification in the Risk Management Plan.
- DE otherwise agrees with the pharmacovigilance activities proposed by the applicant in the PVP along with adverse event reporting as required under 21CFR600.80.
- DE provided comments to the applicant regarding the protocol for the voluntary patient safety registry. In response to the DE comments, the applicant agreed to continue registry enrollment until a minimum of 40 patients has enrolled and at least a five-year period has elapsed.
- The reviewed safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS), a safety postmarketing requirement (PMR) study, or a safety postmarketing commitment (PMC) study at this time.