



## **UTAH MEDICAID DUR REPORT MAY 2018**

### **LUXTURNA (Voretigene neparvovec-rzyl): Gene Therapy for biallelic RPE65 mutation-associated retinal dystrophy**

#### **Drug Regimen Review Center**

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## Introduction

In December 2017, the U.S. Food and Drug Administration (FDA) approved Luxturna (voretigene neparvovec-rzyl), with an orphan drug designation, as the first gene therapy for a genetic disease.<sup>1,2</sup> Three additional gene therapy products are FDA-approved for cancer treatment (i.e., talimogene laherparepvec, axicabtagene ciloleucel, and tisagenlecleucel).<sup>3-5</sup>

Luxturna is administered by subretinal injection and is indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy (e.g., Leber's congenital amaurosis and retinitis pigmentosa).<sup>1,6,7</sup> Luxturna is a gene therapy using a recombinant viral vector to transfer a therapeutic copy of the RPE65 gene into the retinal pigment epithelium (RPE) cells. This gene encodes for the human retinal pigment epithelium 65 kilodalton protein (RPE65), an enzyme that plays an important role in the visual cycle.<sup>8,9</sup>

The purpose of this review is to provide evidence that can assist the Medicaid Drug Utilization Review (DUR) Board in assuring appropriate use of Luxturna in patient populations most likely to benefit.

## Background

### Gene Therapy

The aim of human gene therapy is to treat or cure diseases by modifying defective genes or genetic pathways.<sup>10</sup> Gene therapy approaches may include: (1) replacing a mutant gene by a healthy copy of the gene, (2) inactivating a mutant gene that is operating inappropriately, (3) introducing a new or altered gene to treat the disease.<sup>10</sup>

Gene therapy research is in progress in several countries, particularly in the U.S. and Europe, for multiple diseases including cancer, infectious disease (e.g., human immunodeficiency virus/acquired immune-deficiency syndrome [HIV/AIDS]), monogenic disorders (e.g., patients with aromatic L-amino acid decarboxylase deficiency), movement disorders (e.g., Parkinson's disease), and ocular diseases (e.g., inherited retinal dystrophy due to autosomal recessive mutations in the RPE65 gene).<sup>11</sup>

Gene therapy products can be classified by the vehicle or technology used to deliver the therapeutic gene into the target human cell's genome<sup>10</sup>: (1) plasmid deoxyribonucleic acid (DNA, i.e., circular DNA molecules genetically manipulated), (2) viral vectors (e.g., modified adenoviruses or retroviruses that do not cause infectious diseases and carry the therapeutic gene into target human cells) (3) bacterial vectors (i.e., modified bacteria that do not cause infectious diseases and deliver the therapeutic gene to target cells), (4) human gene editing technology that alters or repairs mutated genes, and (5) patient-derived cellular gene therapy products (i.e., cells extracted from patients, genetically modified, and reintroduced in patient's body).<sup>10</sup>

Biological products for human use such as gene therapy, cellular therapy, and devices associated with gene or cellular therapy are regulated and supervised by the Center for Biologics Evaluation and Research (CBER) within the FDA.<sup>12</sup> Research and development of cellular and gene therapy is rapidly increasing in the U.S. Marketing authorization for these products should be submitted to the

FDA as a biologics license application (BLA). Currently, there are 16 cellular and/or gene therapy products approved by the FDA.<sup>13</sup> Of these 16 therapies, 4 are gene therapies, which are described in **Table 1**.

Table 1. FDA-Approved Gene Therapies

Brand Name (Generic Name)	Formulation	Vector/Technology Used	Indication	FDA Approval
Imlygic <sup>3</sup> (talimogene laherparepvec)	Suspension for intralesional injection	Live, attenuated herpes simplex virus, genetically modified to express huGM-CSF	Melanoma recurrent after initial surgery	October 2015
Kymriah <sup>4</sup> (tisagenlecleucel)	Suspension for intravenous infusion	CD19-directed genetically modified autologous T cell	B-cell precursor acute lymphoblastic leukemia	August 2017
Yescarta <sup>5</sup> (axicabtagene ciloleucel)	Suspension for intravenous infusion	CD19-directed genetically modified autologous T cells	Relapsed or refractory large B-cell lymphoma	October 2017
Luxturna <sup>6</sup> (voretigene neparvovec-rzyl)	Intraocular suspension for subretinal injection	Recombinant adeno- associated virus serotype 2 (AAV2) vector	Confirmed biallelic RPE65 mutation-associated retinal dystrophy	December 2017

## Inherited Retinal Dystrophy Overview

Inherited retinal dystrophies (IRD) are a large class of diseases including several genetic retinal conditions caused by a specific gene mutation in one of more than 220 different genes.<sup>1</sup> IRDs are characterized by visual impairment and may lead to complete blindness over time.<sup>1</sup> IRDs caused by biallelic mutations (both copies of a gene are affected) in the RPE65 gene have a prevalence of 1,000 to 2,000 patients in the United States.<sup>1,14</sup> Eye disorders associated with biallelic RPE65 mutations include several rare diseases, such as retinitis pigmentosa (RP) type 20 and Leber’s congenital amaurosis type 2 (LCA2).<sup>9,15</sup> Clinical diagnosis for the different presentations of biallelic RPE65 mutation-associated retinal dystrophies is challenging due to the heterogeneous nature of these diseases and overlapping symptoms.<sup>8,16</sup>

Clinical diagnosis of IRD can be confirmed by performing a genetic test.<sup>17</sup> According to the American Academy of Ophthalmology, genetic testing can detect the specific mutation causing the disease in up to 60-80% of patients with IRD.<sup>18</sup>

The RPE65 gene provides the instructions for manufacturing the RPE65 protein in the RPE cells.<sup>14,19</sup> The RPE is a monolayer of cells located beneath the photoreceptor cells (rods and cones).<sup>20</sup> It has several functions (e.g., protection against light and free radicals, nutrient transport, and phagocytosis) essential to maintain visual function. In healthy individuals, RPE cells proliferate during early life and remain latent throughout life.<sup>21</sup> As a person ages, there is a slow and progressive loss of RPE cells, with around 2.3% of RPE cells lost per decade of life.<sup>22</sup> The RPE65 protein is produced in the RPE cells and is a key isomerohydrolase in the visual cycle.<sup>9,14</sup>

The visual cycle is a process that constantly regenerates the 11-cis-retinal chromophore, a light-sensitive component of photoreceptor cells that allows the conversion of light into neural signals.<sup>14</sup>

Eventually, these signals are processed as images through the optic nerve.<sup>19,23</sup> Several steps are crucial in the visual cycle, also called visual phototransduction cascade<sup>8,14,24</sup>:

- (1) Light is absorbed by the photoreceptors of the retina (rods, which are activated by dim light and located in peripheral retina, and cones, which are activated by bright light and located in central retina). In the presence of light, 11-cis-retinal is photoisomerized to all-trans-retinal, converting light into electrical signals and initiating vision.
- (2) RPE cells, directly connected to the photoreceptors, produce RPE65 proteins.
- (3) RPE65 proteins act as retinoid isomerohydrolases converting all-trans-retinol into 11-cis-retinol.
- (4) 11-cis retinol is oxidized to the visual chromophore, 11-cis-retinal, allowing the visual cycle to continue operating.

The visual cycle should regularly recycle 11-cis retinal to preserve visual function.<sup>14,24</sup> Mutations in the RPE gene cause a reduction or lack of RPE65 protein levels, preventing the regeneration of 11 cis-retinal in the visual cycle. This leads to a loss of photoreceptor cells, visual disturbances, and ultimately total blindness.<sup>8,24</sup> Several point mutations in the RPE65 gene have been identified.<sup>9</sup> Each point mutation may cause different deficits in RPE65 protein levels and thereby, different stages of disease severity.<sup>9</sup>

### Retinitis pigmentosa

Retinitis pigmentosa (RP) is a heterogeneous group of inherited rod-cone dystrophies that cause degeneration of the photoreceptor cells in the retina (rods and cones) and may progress to complete visual loss.<sup>8,16,25-27</sup> A consolidated classification for RP is not yet established.<sup>8</sup> Retinitis pigmentosa can be classified based on the cells and tissues affected as nonsyndromic RP (RP mainly affecting the eye) or syndromic RP (RP with systemic manifestations).<sup>8</sup> Retinitis pigmentosa can be additionally classified by the type of inheritance as autosomal dominant (15–25%), autosomal recessive (5–20%), X-linked (5–15%), or unknown (40–50%).<sup>8</sup> More than 3000 mutations in approximately 70 different genes have been associated with RP.<sup>8</sup> These mutations can interfere with the normal function of photoreceptors cells and RPE cells. Retinitis pigmentosa is characterized by abnormal black deposits of accumulated pigment (“bone spicules”) in the peripheral retina, reducing the capacity to perceive light.<sup>8,25</sup> Clinical manifestations include nyctalopia (night blindness), visual acuity deterioration, narrowed peripheral visual field (tunnel vision), and anomalous electroretinogram.<sup>25,26</sup> Clinical diagnosis may involve fundus examination, visual field test, ophthalmic examination, and multifocal electroretinography.<sup>8,16</sup> Daily living activities such as walking and driving in areas with low light are compromised in patients with RP.<sup>8</sup> Night vision is typically affected in adolescence due to rod degeneration, peripheral vision decreases in young adulthood, and loss of central vision due to cone degeneration occurs in later life.<sup>8,26</sup>

Autosomal recessive retinitis pigmentosa type 20 (RP20) is the form of the disease related to biallelic (homozygous or compound heterozygous) mutation in the RPE65 gene.<sup>16,28</sup>

Around 2.5 million people are diagnosed with RP worldwide.<sup>8</sup> The prevalence of RP in the US and Europe is around 1:3,500 to 1:4,000.<sup>16</sup> Among all cases of nonsyndromic autosomal recessive RP, 2% to 5% are associated with RPE65 mutations.<sup>8,16</sup>

## Leber's congenital amaurosis

Leber's congenital amaurosis (LCA) is an autosomal recessive childhood condition affecting rods and cones in the retina and is the most common genetic eye disorder among children.<sup>29</sup> It is one of the most severe types of IRD, with substantial visual impairment or blindness at birth or early after birth, nystagmus (uncontrolled, rapid, and repetitive eye movements), amaurotic pupils (abnormal pupils unresponsive to direct light), and lack of electroretinogram signals.<sup>17,30,31</sup> Clinical diagnosis is typically based on these features; however, universal agreed diagnostic criteria are lacking.<sup>32</sup> LCA can result from mutations in 19 different genes (e.g., CRB1, LRAT, RPE65, and GUCY2D).<sup>19,31</sup> LCA and RP share many mutated genes; thereby, LCA is considered a subtype of retinitis pigmentosa presenting with more severe visual impairment or blindness, earlier onset (beginning in the first year of life), and nystagmus.<sup>19,27,29</sup> Visual acuity in patients with LCA typically ranges from 20/200 (severe visual impairment) to light perception or no light perception; however, some patients may experience temporary visual improvements.<sup>31</sup> Eventually, LCA patients develop complete blindness by "mid to late adulthood".<sup>31</sup>

Mutations in the RPE65 gene are one of the most studied causes of LCA.<sup>19</sup> Leber congenital amaurosis type 2 (LCA2) is the form of the disease related to biallelic RPE65 mutations.<sup>33</sup> A mild form of LCA2 has been described with different names, including early-onset severe retinal dystrophy (EOSRD), severe early childhood-onset retinal dystrophy (SECORD), or early-onset RP.<sup>34,35</sup>

LCA prevalence is approximately 2 to 3 per 100,000 births.<sup>32</sup> All LCA cases account for 5% of all retinal dystrophies.<sup>14,32</sup> Among all cases of LCA, 3% to 16% are associated with RPE65 mutations (i.e., LCA2).<sup>32</sup> Around 20% of children attending schools for the blind have LCA.<sup>31</sup>

## Natural history study of inherited retinal dystrophies due to RPE65 mutations

A retrospective natural history study of RPE65 mutation-associated retinal dystrophies was conducted by the drug sponsor. A total of 70 subjects diagnosed with LCA (58%), early-onset severe retinal dystrophy (5%), severe early-childhood onset retinal dystrophy (7%), RP (8%), and tapetal retinal dystrophy (14%) were evaluated in this study. Study results indicated an age-related progressive worsening of visual acuity and visual fields, with patients experiencing complete blindness in their early twenties.<sup>7</sup>

## **Methodology**

We searched PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Clinical Trials.gov, and the US FDA website for specific information related to voretigene neparvovec and the management of retinal dystrophies due to RPE65 mutations. Additional drug information resources, such as Lexicomp and Micromedex were also consulted.

Utilization data was queried for all patients, looking at claims related to the product's National Drug Code (NDC). We attempted to search Luxturna by Common Procedural Terminology (CPT) codes; however these codes were too general to capture the administration of Luxturna. No specific International Statistical Classification of Diseases and Related Health Problems (ICD)-10 code for biallelic RPE65 mutation-associated retinal dystrophy was identified.

## Treatment Options

Luxturna is the first therapy approved for the treatment of patients with biallelic RPE65 mutation-associated retinal dystrophy. Luxturna helps to improve visual function, but does not cure the condition. It is administered as a single injection in each eye and no long-term efficacy and safety data are currently available. An extension of the phase 3 study is ongoing and will follow patients for 15 years. No other gene therapies or pharmacological treatment options are currently available for this rare genetic disease.<sup>7</sup> Luxturna is only approved in the US.<sup>7</sup>

A retinal device (i.e., Argus II Retinal Prosthesis System) is FDA-approved for severe retinitis pigmentosa.<sup>7</sup> It is a retinal implant that electrically stimulates the retina, inducing visual perception in blind individuals.<sup>7</sup>

## Search Results

Several FDA reports and clinical information request letters were identified on the FDA website. In addition, multiple publications including results from phase 1 and phase 3 studies are available. A summary of the clinical FDA review for Luxturna approval is outlined in the “Clinical Aspects” section of this report.

The following information was considered to prepare this report:

- FDA Information for Luxturna (see “Clinical Aspects” section of this report):
  - o Clinical Review<sup>7</sup> (December 16, 2017)
  - o Summary Basis for Regulatory Action<sup>15</sup> (December 18, 2017)
  - o Approval Letter<sup>2</sup> (December 19, 2017)
- Published Clinical Trials (see **Appendix B**)
  - o Russell et al<sup>19</sup> (2017): Phase 3 pivotal study in patients with RPE65-mediated inherited retinal dystrophy
  - o Maguire et al<sup>36</sup> (2009): Phase 1 study in patients with RPE65-mediated inherited retinal dystrophy (first-treated eye)
  - o Bennett et al<sup>37</sup> (2016): follow-on phase 1 trial (treatment of contralateral eye)

## Luxturna (voretigene neparvovec-rzyl) for Retinal Dystrophy

### Luxturna (voretigene neparvovec-rzyl)

Voretigene neparvovec-rzyl (voretigene) is an intraocular suspension containing a genetically modified adeno-associated virus type 2 (AAV2) that carries a therapeutic RPE65 gene encoding for the RPE65 protein.<sup>6,7,15</sup> This vector is a live and replication-defective virus capable of infecting RPE cells without causing infectious diseases. Following the subretinal injection of voretigene close to the RPE cells of patients with RPE65 mutations, voretigene is intended to deliver free healthy copies of the RPE65 gene into the nucleus of RPE cells, leading to RPE65 protein production.<sup>7,15</sup> This protein plays a key role in the regeneration of retinal light-sensitive proteins essential for normal vision.<sup>7,15</sup>

The injection is approved for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy without limitation to a particular phenotype (e.g., LCA2 or autosomal recessive RP). Information from the FDA-approved Luxturna label is summarized in **Table 2**.

Table 2. Luxturna Indications, Dosing, and Use Concerns<sup>6</sup>

<b>FDA Approval Date</b>	December 2017
<b>Product Description</b>	<ul style="list-style-type: none"> <li>• Luxturna (voretigene neparvovec-rzyl) is a gene therapy including the following characteristics:               <ul style="list-style-type: none"> <li>- Formulation: intraocular suspension</li> <li>- Vector used: genetically modified adeno-associated virus serotype 2 (AAV2)</li> <li>- Administration: subretinal injection</li> </ul> </li> <li>• <i>Dosage Form</i>: single-dose 2 mL vial (with 0.5-mL extractable volume) for a single administration in one eye. The supplied concentration (<math>5 \times 10^{12}</math> vg/mL) requires a 1:10 dilution prior to administration. The Diluent is supplied in two single-use 2 mL vials</li> <li>• <i>Storage</i>: Store intact vial and diluent frozen at <math>\leq -65^{\circ}\text{C}</math> (<math>\leq -85^{\circ}\text{F}</math>). Store thawed vials at room temperature. Diluted solution should be stored at room temperature during delivery to surgical suite.</li> </ul>
<b>FDA Labeled Indication</b>	Treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s)
<b>Pediatric Use</b>	Not recommended for patients < 12 months of age
<b>Dosage &amp; Administration</b>	<ul style="list-style-type: none"> <li>• Recommended dose for each eye: <math>1.5 \times 10^{11}</math> vg in a total volume of 0.3 mL</li> <li>• Subretinal administration of Luxturna should be performed to each eye on separate days within a close interval, but no fewer than 6 days apart</li> <li>• Systemic oral corticosteroids are recommended: corticosteroids equivalent to prednisone at 1 mg/kg/day (maximum of 40 mg/day) for a total of 7 days (starting 3 days before administration of Luxturna to each eye), and followed by a tapering dose during the next 10 days</li> </ul>
<b>Contraindications</b>	None
<b>Warnings &amp; Precautions</b>	<ul style="list-style-type: none"> <li>• <i>Endophthalmitis</i>: may occur following intraocular surgical procedure or injection. Proper aseptic injection technique should be used. Monitor for signs or symptoms of infection or inflammation</li> <li>• <i>Permanent decline in visual acuity</i>: may occur following subretinal injection. Monitor for visual disturbances</li> <li>• <i>Retinal abnormalities</i>: e.g. macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. May occur during or after subretinal injection. Monitor appropriately. Avoid administration in immediate vicinity of fovea.</li> <li>• <i>Increased intraocular pressure</i>: may occur following subretinal injection. Monitor for IOP</li> </ul>



Table 2. Luxturna Indications, Dosing, and Use Concerns<sup>6</sup>

	<ul style="list-style-type: none"> <li>• <i>Expansion of intraocular air bubbles</i>: it may lead to irreversible vision loss. Avoid air travel, travel to high elevations or scuba diving until air bubble has completely dissipated (may take 1 week or more following injection)</li> <li>• <i>Cataract</i>: subretinal injection (especially vitrectomy surgery) may increase the incidence of cataract development or progression.</li> </ul>
<b>Adverse Reactions</b>	<ul style="list-style-type: none"> <li>• Adverse reactions with incidence <math>\geq</math> 5%:             <ul style="list-style-type: none"> <li>- conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula)</li> </ul> </li> <li>• Immunogenicity: mild immune reactions</li> </ul>

Abbreviation: IOP, intraocular pressure; vg, vector genome

### Luxturna Preparation and Injection Procedure

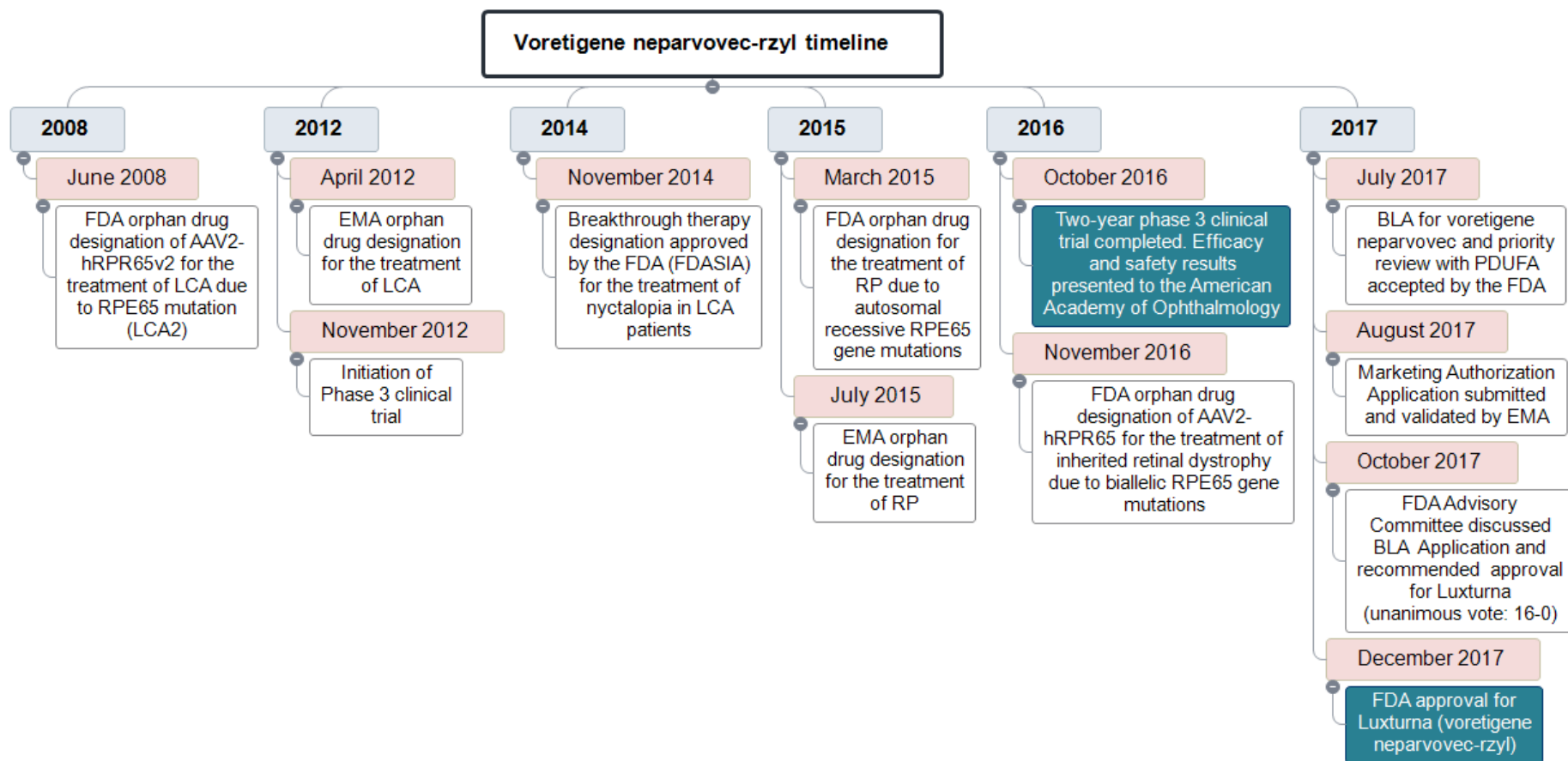
Luxturna should be diluted to the appropriate concentration ( $1.5 \times 10^{11}$  vector genomes) 4 hours before administration.<sup>6</sup> Instructions for the preparation of Luxturna suspension are described in the package insert.<sup>6</sup>

The subretinal injection procedure requires the syringe containing diluted Luxturna, a subretinal injection cannula, and a specific extension tube.<sup>6</sup> Under general anesthesia, a standard vitrectomy procedure (e.g., posterior pars plana vitrectomy) should be undertaken before administering Luxturna subretinally (via pars plana).<sup>6,7</sup> Surgical procedure and injection of Luxturna should be performed by a surgeon with experience in intraocular procedures.<sup>6</sup>

### Clinical Aspects

A BLA for voretigene neparvovec-rzyl was submitted to the FDA in April 2017.<sup>7,15</sup> A priority review, breakthrough therapy, and orphan drug designations were granted by the FDA.<sup>7,15</sup> In December 2017, Luxturna was approved for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy.<sup>1,2,7,15</sup> A regulatory timeline concerning voretigene neparvovec-rzyl is presented in **Figure 1**.

Figure 1. Regulatory Timeline<sup>7,15,38</sup>



Abbreviations: AAV2-hRPR65v2, adeno-associated viral vector type 2-human recombinant retinal pigment epithelial 65 kDa; BLA, Biologics License Application; EMA, European Medicines Agency, FDA, Food and Drug Administration, FDASIA, Food and Drug Administration Safety and Innovation Act, LCA, Leber’s congenital amaurosis; PDUFA, Prescription Drug User Fee Act; RP, retinitis pigmentosa

I. Clinical Development Program for voretigene neparovec-rzyl (BLA submission)<sup>7,15</sup>

The BLA submission for Luxurna approval was mainly based on a phase 1 study with 2 protocols (Study 101 and 102) and a phase 3 study with 2 parts (Study 301 and 302). Both studies provided safety data and the phase 3 study was the pivotal trial contributing to the efficacy of Luxturna.

Table 3. Clinical Program for Voretigene Neparovec-rzyl<sup>7,15</sup>

Study Design	Primary objective	Design/Duration	N	Intervention <sup>a</sup>
Phase 1 clinical study with 2 protocols (Studies 101 and 102)	Study 101: To determine the safety and tolerability of 3 doses in 1 eye ( <i>first-treated eye, chosen with worse function</i> )	<b>Study 101:</b> Open-label, dose-escalation safety study  Study period: 2007-2014	<b>12</b> patients (≥8 years old) with LCA due to RPE65 mutations (homozygotes or compound heterozygotes)  Age range: 8-44 years	Patients received a single dose of one of the following 3 strengths: <ul style="list-style-type: none"> <li>• 1.5 x 10<sup>10</sup> vg (3 patients)</li> <li>• 4.8 x 10<sup>10</sup> vg (6 patients)</li> <li>• 1.5 x 10<sup>11</sup> vg (3 patients)</li> </ul>
	Study 102: To determine the safety and tolerability of treatment to contralateral eye ( <i>second-treated eye</i> )	<b>Study 102:</b> Follow-on study  Study period: 2010-2014	<b>11</b> patients from Study 101	11/12 patients received 1 high dose (1.5 x 10 <sup>11</sup> vg) in a total volume of 300 µL in the contralateral eye (injection interval between eyes: 1.7 to 4.6 years)
Phase 3 clinical study with 2 parts (Studies 301 and 302)  <i>Setting:</i> 2 sites in the U.S.  Study Duration: 2 years + 13 years of follow-up	To evaluate efficacy and safety of sequential subretinal injection of voretigene neparovec to each eye	<b>Study 301</b> (main study): Open-label, randomized, controlled trial  Duration: 1 year (primary efficacy outcome measured at 1 year)  <b>Study 302</b> (cross-over study): after the first year, all patients received Luxturna  Duration: 1 year (outcomes measured at 2 years after entry to study 301)	<b>31</b> patients (≥ 3 years old) with LCA due to RPE65 mutation(s) in both alleles  Age range: 4-44 years  • ITT (N=31)  • mITT (N=29) (2 patients discontinued study 301, 1 in each group)	<ul style="list-style-type: none"> <li>• Treatment group (voretigene): 21 patients (20 patients received voretigene in the second eye, with injection interval of 6 to 18 days)</li> <li>• Control (no intervention): 10 patients (2:1 randomization)</li> <li>• Cross-over group: 9/10 patients in the control group of Study 301 crossed over to receive injection of voretigene (injection interval between eyes: 7 to 14 days)</li> </ul>

Abbreviations: BL, baseline; CS, corticosteroids; ITT, intention-to-treat population; mITT, modified intention-to-treat population, LCA, Leber congenital amaurosis; MLMT, multi-luminance mobility testing (ranging from 0 to 6); N, number of patients; vg, vector genomes

<sup>a</sup> All patients treated with voretigene received short course of oral corticosteroids (prednisolone 1 mg/kg/day starting 3 days before the first-eye injection and continued for a total of 7 days)

## II. Published Phase 3 Trial Information<sup>7,15</sup>

Table 4. Phase 3 Trial Design<sup>7,15</sup>

Inclusion Criteria	<ul style="list-style-type: none"> <li>• ≥3 years of age</li> <li>• Diagnosis of Leber congenital amaurosis due to RPE65 mutation(s) in both alleles</li> <li>• VA 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</li> <li>• Able to perform a MLMT, but unable to pass the MLMT at 1 lux, the lowest luminance level tested</li> </ul>
Exclusion Criteria	<ul style="list-style-type: none"> <li>• Subjects with insufficient viable retinal cells as determined by OCT, e.g., areas of retina with thickness measurements less than 100 μm, or absence of neural retina</li> <li>• Intraocular surgery within prior six months</li> </ul>
Study Sites	<ul style="list-style-type: none"> <li>• The Children’s Hospital of Philadelphia, Philadelphia, PA (CHOP)</li> <li>• University of Iowa Hospitals and Clinics, Iowa City, IA (IA)</li> </ul>
Study Treatment	<ul style="list-style-type: none"> <li>• Intervention: One dose, 1.5 x10<sup>11</sup> vg/300 μL, administered by subretinal injection. Additionally, oral prednisone was given (1 mg/kg/day with a maximum dose of 40 mg/day, starting 3 days before the first-eye injection and continued for a total of 7 days) to reduce any immune response to AAV2 capsid and RPE65. Peri-ocular CS injections were not allowed</li> <li>• Control: no investigational product or corticosteroids were given</li> </ul>
Study Duration	<ul style="list-style-type: none"> <li>• Study 301: 1 year</li> <li>• Study 302: one additional year to the Study 301</li> <li>• Long-term follow-up: 13 years (Total: 15 years)</li> </ul>
Monitoring	<p>First year:</p> <ul style="list-style-type: none"> <li>• Patients received voretigene neparvovec at Day 0</li> <li>• Safety and efficacy assessments in both groups at Days 30, 90, 180, and one year</li> </ul> <p>Year 2 to 5: annual visits to assess safety and efficacy</p> <ul style="list-style-type: none"> <li>• Physical examination, including vital signs</li> <li>• Blood and urine tests</li> <li>• Ophthalmic examination, including fundus photography and OCT</li> <li>• Mobility testing</li> <li>• Other visual/retinal function testing</li> <li>• Clinical questionnaire</li> </ul> <p>Year 6-15:</p> <ul style="list-style-type: none"> <li>• Annual phone contact or visit, mainly for clinical questionnaire</li> </ul>
Endpoints (Including changes recommended by the FDA before Phase 3 data lock)	<p><u>Primary efficacy endpoint:</u> co-primary endpoint of both the MLMT score change using both eyes and MLMT score change using the first-treated eye from baseline to 1 year</p> <p><u>Secondary endpoints:</u> (analysis of each eye separately)</p> <ul style="list-style-type: none"> <li>• Change in FST using white light, as measured by the averaged FST of two eyes at Year 1</li> <li>• MLMT score change using the first eye from baseline to Year 1</li> <li>• Change in VA as measured by the averaged change in VA of the two eyes at Year 1</li> </ul> <p><u>Safety endpoints:</u></p> <ul style="list-style-type: none"> <li>• Incidence of AEs and SAEs, which were assessed by adverse event recording, routine physical exams and ophthalmic evaluations, and routine laboratory tests such as serum chemistry and hematology</li> <li>• 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</li> </ul>

Abbreviation: AAV2, adeno-associated viral vector type 2; AE, adverse events; CS, corticosteroid; ELISPOT, Enzyme-Linked Immunospot Assay; FST, full-field light sensitivity threshold testing; ITT, intention-to-treat; MLMT; lux, lumens/m<sup>2</sup>; multi-luminance mobility testing; OCT, optical coherence tomography; SAE, serious adverse events; PBMC, peripheral blood mononuclear cells; VA, visual acuity; vg, vector genome

- Demographic characteristics

The mean age of the 31 included subjects was 15 years old (age range: 4 to 44 years), with 14 subjects (45%) between 4 and 10 years old, 6 subjects (19%) between 11 and 17 years old, and 11 subjects (36%) older than 17 years old. There were marginally more females than males and the majority were white (68%). Baseline mobility performance was measured at different light levels, with 52% of patients passing the mobility test at <125 lumen/m<sup>2</sup> and 48% at ≥125 lumen/m<sup>2</sup>.

- Subject disposition

Two of the 31 patients randomized discontinued the study, one in the treatment group before receiving voretigene neparvovec due to severe retinal degeneration, and one in the control group at screening visit due to patient’s withdrawal.


- Primary efficacy endpoint

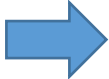
The phase 3 pivotal trial used an innovative efficacy endpoint, the multi-luminance mobility testing (MLMT), which aimed to assess the functional vision. The MLMT was developed and validated by the drug sponsor for this specific clinical program. This test consists of a navigation course with several obstacles (e.g., steps, holes, grass, and foam), arrows, and turns to examine time spent on finishing the course and accuracy to avoid the obstacles within the circuit. Twelve randomized navigation courses were used to evaluate patient’s mobility during the trial. This MLMT was performed under 7 different lighting conditions (1, 4, 10, 50, 125, 250 and 400 lumen/m<sup>2</sup>); where 1 lumens/m<sup>2</sup> represented a moonless summer light level and 400 lumen/m<sup>2</sup> represented the light similar to an office setting.

In the first year, patients performed the MLMT at days 30, 90, 180, and 365 with one eye covered, the other eye covered, and without any eye covered. At least 2 luminance levels were used.

Evaluation of patient’s mobility was determined by the MLMT score codes, which ranged from -1 (if patients did not pass the test at the highest light level conditions) to 6 (if patients passed the test at the lowest light level conditions).

Table 5. Correlation between luminance level (Lux) and MLMT score code

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



The difference between the baseline score and the final score at each time point is the MLMT score change. The **primary efficacy endpoint** was defined as **the median MLMT score change from baseline to year 1 using both eyes and the first treated-eye (co-primary endpoint)**. The phase 3 trial was open-label, however, the 2 evaluators assessing the MLMT performance were blinded. The FDA determined an MLMT score change ≥ 2 as clinically relevant.

The assessment of the primary efficacy endpoint using all randomized subjects (i.e., intention-to-treat population [ITT]) was recommended by the FDA. A modified ITT population (excluding the 2 patients that discontinued the study) and per protocol (PP) populations were considered for sensitivity and supportive efficacy analyses.

### III. Key Phase 3 Efficacy Findings<sup>7,15</sup>

#### - Primary efficacy outcomes

With regard to the primary efficacy outcomes, patients treated with voretigene neparvovec showed statistically significant and clinically relevant score changes from baseline to one year in the MLMT performance, compared to the control group. Among the 21 patients treated with voretigene neparvovec, 52% (11/21) had an MLMT score  $\geq 2$  using both eyes versus 10% (1/10) patients in the control group. When patients used individual eyes, 71% of patients in the treatment group versus 0% patients in the control group had an MLMT score  $\geq 2$ .

During the second year, in the group treated with voretigene neparvovec, there was a sustained treatment effect (the median MLMT score change of 2 remained over the 2-year period). Patients crossing-over from the control group to voretigene neparvovec after year 1 showed similar MLMT improvements to the patients who started with voretigene neparvovec at Day 0.

Table 6. Phase 3 Clinical Trial Efficacy Results

Phase 3 clinical study	Primary efficacy endpoint (ITT population): Median change in MLMT performance from BL to 1 year (functional vision) using both eyes and the first-treated eye				
	MLMT median score change	Luxturna (N=21)	Control (N=10)	Difference (Luxturna minus control)	P-value
	Both eyes, median (min, max)	2 (0, 4)	0 (-1, 2)	2	0.001
	First treated-eye, median (min, max)	2 (0, 4)	0 (-1, 1)	2	0.003

Abbreviations: BL, baseline; ITT, intention-to-treat; mITT, modified intention-to-treat; MLMT, multi-luminance mobility testing (ranging from 0 to 6); N, number of patients; VA visual acuity;

#### - Secondary efficacy outcomes

Full-field light sensitivity threshold testing (FST) score change from baseline to year 1 was the key secondary endpoint. FST evaluated patient's perception of different white lighting levels. Results showed a significant light sensitivity improvement from baseline to year 1 in the voretigene group compared to control group. This improvement was observed at day 30 and remained for 2 years.

The change in visual acuity from baseline to year 1 was also measured as a secondary endpoint. No significant differences between voretigene and control groups were reported.

### IV. Key Phase 3 Safety Findings

Safety analysis was based on the combined population from Phase 1 and Phase 3 that received at least one injection of voretigene in either eye (i.e., 41 patients: 12 patients from phase 1 and 29 patients from phase 3). Among the 41 patients, 40 received injections in both eyes.

Ocular adverse reactions were described in 66% of patients, being conjunctival hyperemia (9/41, 22%), cataract (8/41, 20%), increased intraocular pressure (6/41, 15%), and retinal tear (4/41,

10%) reported with an incidence of 10% or higher. The majority of these adverse events were associated with the ocular surgical procedure and subretinal injection, and were transient and medically manageable. Two serious adverse events related to the injection procedure (i.e. endophthalmitis and permanent loss of vision) were reported in 1 patient each. Systemic adverse events such as hyperglycemia, hypoglycemia, nausea, and sickness were probably associated with the use of oral corticosteroids and reactions to anesthesia.

Immune reactions against adeno-associated virus capsid or RPE65 were mild, and considered by investigators to be likely due to the use of oral corticosteroids.

#### V. FDA Advisory Committee Meeting Conclusions and Recommendations

The 16 members of the Advisory Committee concluded that the benefit-risk balance for Luxturna in patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy is positive.

#### VI. Postmarketing Activities<sup>7,15,39</sup>

Pharmacovigilance measures proposed by the drug sponsor were accepted by the FDA. The postmarketing risk management plan includes:

- An ongoing long-term follow-up study of all patients receiving Luxturna in clinical trials (Total study duration: 15 years, end of study: 2029). Efficacy data, adverse events related to Luxturna or injection procedure, and adverse events such as the occurrence of oncologic, hematologic, neurologic, and auto-immune diseases will be collected and monitored. Annual updates will be reported.
- A 5-year follow-up patient safety registry of at least 40 patients. This study will provide long-term safety information
- Routine pharmacovigilance plan for adverse event reporting
- Pharmacists' training concerning the preparation of voretigene neparvovec suspension, and surgeons' training regarding subretinal administration

No Risk Evaluation and Mitigation Strategy (REMS), a safety postmarketing requirement (PMR), or a safety postmarketing commitment (PMC) study were considered necessary.<sup>39</sup>

## Utah Medicaid Utilization Data

The Utah Medicaid Utilization Data documented no utilization of the new gene therapy, Luxturna. There is no specific ICD-10 diagnosis code for the biallelic RPE65 mutation-associated retinal dystrophy. However, we explored more broadly patients with ICD-10 diagnosis codes for retinal dystrophy. For informational purposes, **Table 7** includes the number of patients with diagnosis codes submitted for retinal dystrophies. It is unclear whether these patients have biallelic RPE65 mutation-associated retinal dystrophy (e.g., autosomal recessive RP type 20 and LCA type 2) and may be potentially qualified to receive Luxturna.

Table 7. Number of Patients with Diagnosis Codes Submitted for Retinal Dystrophy

	Diagnosis Code Submitted	Unique Patients
ACO	H3550-Unspecified hereditary retinal dystrophy	3
	H3552-Pigmentary retinal dystrophy	18
	H3554-Dystrophies primarily involving the retinal pigment epithelium	15
FFS	H3550-Unspecified hereditary retinal dystrophy	6
	H3552-Pigmentary retinal dystrophy	6
	H3554-Dystrophies primarily involving the retinal pigment epithelium	14
Total Unique Patients		58

Abbreviations: ACO, accountable care organizations; FFS, fee-for-service



## Discussion Topics for Developing Prescribing Criteria

### Potential Prior Authorization Criteria for Luxturna

1. FDA-approved indication, molecular diagnosis, and appropriate selection of potential responders to treatment

The FDA prescribing labeling information includes the following indication for Luxturna:

“Treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s).”

Documentation for the subsequent points is suggested:

- **Genetic testing** to confirm the presence of biallelic RPE65 mutations (homozygotes or compound heterozygotes).

*Notes from the FDA Clinical Review:*

- o All patients included in phase 1 and phase 3 studies received a genetic diagnosis confirmation for this specific gene mutation before initiating the studies. Clinical Laboratory Improvement Amendments (CLIA)-certified molecular diagnosis laboratories conducted the genetic tests.<sup>7</sup>
- o Luxturna is approved for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy without limitation to a particular phenotype (e.g., LCA2 or autosomal recessive RP). Phase 1 and phase 3 studies only included patients with LCA2, a subtype of RP. Retinal dystrophies associated with RPE65 gene mutations include a diverse group of genetic eye disorders with several clinical presentations. Clinical diagnosis is challenging and a molecular genetic diagnosis is required to determine the correct diagnosis. LCA is characterized by severe vision loss beginning in early life and rapid progression. RP onset may appear later in life, and is characterized by a slow progression of visual impairment. As there are several clinical diagnoses under the umbrella of retinal dystrophies associated with RPE65 gene mutations, the FDA considered that the indication for Luxturna should be defined based on the molecular genetic diagnosis (i.e. presence of biallelic RPE65 mutations) instead of the clinical diagnosis (e.g., LCA and RP)<sup>7</sup>

- **Presence of viable retinal cells** using ophthalmologic assessment techniques as determined by the treating physician.

*Note from the FDA Clinical Review:* The Phase 3 trial used optical coherence tomography (OCT) to evaluate the presence of viable retinal cells in each patient and determine if patients may or may not respond to treatment. However, the FDA questioned the accuracy of OCT technique because the relationship between the thickness of the retina and the viability of retinal cells is unclear (3/20 patients evaluated by OCT did not respond to voretigene neparvovec in clinical trials).<sup>7</sup> The indication of Luxturna, as stated in the package insert, include that patients “must have viable retinal cells as determined by the treating physician(s)”. No reference to the use of OCT to identify patients that may respond to treatment is cited in the package insert.

## 2. Population (restriction by age)

The FDA-approved labeling states that the administration of Luxturna is not recommended in pediatric patients younger than 12 months of age because proliferation of retinal cells is still occurring, and the effect of Luxturna can be reduced. For geriatric use, no efficacy and safety data for Luxturna are available in this population.

*Note from the FDA Clinical Review:* The phase 3 study for Luxturna included patients from 4 to 44 years old, although the planned protocol allowed inclusion of patients of 3 years old and older.<sup>7</sup> The phase 1 study included patients from 8 to 44 years old. No clinical data seem to be available for patients between 1 year old and less than 4 years old.

## 3. Administration

- **Single injection in each eye** - The efficacy and safety of repeated administrations in the eyes already treated with Luxturna have not been established
- Subretinal injection only
- Luxturna should be administered by subretinal injection in each eye on separate days, with at least a 6-day interval
- **Administration should be performed by surgeons with experience in intraocular surgery**
- Patients must not have had intraocular surgery within 6 months prior to voretigene administration
- Preparation of Luxturna suspension under aseptic conditions and within 4 hours before administration

*Note from the FDA Clinical Review:* The pharmacovigilance plan proposed for Luxturna contains pharmacists' training concerning the appropriate preparation of Luxturna suspension and healthcare professionals' training for the correct administration of the product.<sup>7</sup>

## Summary

Inherited retinal dystrophies (IRD) encompass a large class of genetically and phenotypically heterogeneous conditions that may progress to complete blindness. IRD caused by biallelic mutations in the RPE65 gene have a prevalence of 1,000 to 2,000 patients in the United States, and include Leber congenital amaurosis type 2 and autosomal recessive retinitis pigmentosa. Luxturna (voretigene neparvovec-rzyl) received an orphan designation for the treatment of IRD due to biallelic RPE65 gene mutations in November 2016, and was approved for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy in December 2017.

Voretigene neparvovec-rzyl is a gene therapy product that uses an adeno-associated virus type 2 (AAV2) vector to deliver a healthy copy of the RPE65 gene in the RPE cells. When this product is administered via subretinal injection, the RPE65 gene encodes the RPE65 protein, leading to improvements in the light perception and visual function.

A single Phase 3 clinical trial in 31 patients (age range: 4 to 44 years old) with biallelic RPE65 mutation-associated retinal dystrophy was conducted to compare a voretigene neparvovec-rzyl treated group with a control group. Patients treated with voretigene showed a statistically and clinically relevant improvement in the ability to navigate autonomously in dim luminance conditions compared to control group, as reported by the primary efficacy endpoint (i.e., median Multi-Luminance Mobility Testing score change from baseline to year 1 using both eyes and the first treated-eye). Improvement in responders remained stable for at least 2 years after treatment. Secondary efficacy outcomes supported the favorable primary efficacy outcomes. These improvements in the visual function may indicate the restoration of the visual cycle due to RPE65 proteins activity. Long-term efficacy profile in terms of maintenance of effect and progressive retinal degeneration are currently unknown.

The main adverse events are primarily related to the subretinal injection (e.g., conjunctival hyperemia, cataract, increased intraocular pressure, and retinal tear) and coadministration of systemic corticosteroids (e.g., hyperglycemia). Most of adverse events were mild, transient, and manageable with adequate treatment or surgical procedure. Long-term safety profile is currently uncertain. A postmarketing risk minimization plan was proposed to minimize these risks and collect long-term safety data.

Luxturna was approved in December 2017 and no other pharmacological therapies are currently available for this genetic disease. The Utah Medicaid utilization data documented no utilization for the new ocular gene therapy, Luxturna. To optimize and control future usage, a prior authorization assessment based on the FDA-approved indication (defined by molecular diagnosis), target population, and administration concerns, is warranted. The purpose of the prior authorization is to encourage appropriate prescribing so that newer treatment options are considered only in those patients where medically necessary and appropriate.

## Appendix A: Relevant ICD-10 Diagnosis Codes and CPT Codes

ICD-10 Codes	
ICD-10 Diagnosis Code	Diagnosis
H3550	UNSPECIFIED HEREDITARY RETINAL DYSTROPHY
H3552	PIGMENTARY RETINAL DYSTROPHY
H3554	DYSTROPHIES PRIMARILY W THE RETINAL PIGMENT EPITHE

Abbreviation: ICD-10, International Classification of Diseases, Tenth Revision

CPT Codes	
CPT <sup>a</sup> Code	Procedure
67036	VITRECTOMY,MECH., PARS PLANA APPROACH
67299	UNLISTED PROCEDURE, POSTERIOR SEGMENT

Abbreviation: CPT, Common Procedural Terminology

<sup>a</sup> CPT codes may be accompanied by RT (right eye) or LT (left eye) to identify the eye receiving Luxturna

Note: ICD-10 and CPT codes included in tables 1 and 2 were suggested by Spark Therapeutics

## Appendix B: Key Findings in Published Clinical Trials

Table 1. Published Clinical Trials for Luxturna

Study Reference and Design	Population	Efficacy and Safety Findings
Russell, <sup>19</sup> 2017 Open-label randomized controlled Phase 3 trial (NCT: 00999609)	31 patients with RPE65 mutation-associated LCA  (both eyes treated)  • ITT population: ○ Intervention (n=21) ○ Control (n=10) • Modified ITT: ○ Intervention (n=20) ○ Control (n=9)	<i>Primary efficacy endpoint</i> (mean bilateral MLMT change score at 1 year):  • Intervention: 1.8 (SD 1.1) light levels • Control: 0.2 (SD 1.0) light levels • Difference between groups: 1.6, 95% CI 0.72-2.41, <b>p=0.0013</b> • 13/20 (65%) in the intervention group vs. 0% in control group passed MLMT at the lowest luminance level tested (1 lux), which is the maximum possible improvement  <i>Safety:</i>  • No product-related SAE or deleterious immune responses • 2 intervention participants had SAEs unrelated to study participation • Most ocular events mild in severity
Maguire, <sup>36</sup> 2009 Phase 1 dose-escalation study (NCT: 00516477)	12 patients with RPE65 mutation-associated LCA  (first treated-eye)  • 3 doses tested	• Voretigene neparvovec well tolerated • Improvement in subjective and objective measurements of vision (i.e., dark adaptometry, pupillometry, electroretinography, nystagmus, and ambulatory behavior) remained stable in all patients  • “Patients with at least a 2 log unit increase in pupillary light responses” • “An 8-year-old child had nearly the same level of light sensitivity as that in age-matched normal-sighted individuals”  • Greatest improvement reported in children (all gained ambulatory vision)
Bennett, <sup>37</sup> 2016 Follow-on Phase 1 study (NCT: 01208389)	11 patients with RPE65 mutation-associated LCA  (contralateral eye)  (RPE65 mutation-associated LCA)  • Dose administered: $1.5 \times 10^{11}$ vector genome	• No adverse events related to the AAV • Mild adverse events related to the procedure: 3 patients with dellen formation and 2 with cataracts • 1 patient experienced bacterial endophthalmitis (excluded from analyses) • Most patients with improvements in efficacy outcomes and without significant immune response  <i>Injected contralateral eye:</i>  • Mean mobility test: pooled analysis of 10 subjects showed improvements from baseline to day 30, that continued to year 3, (p=0.0003) • Full-field light sensitivity: pooled analysis of 10 participants showed improvements from baseline to day 30, that continued to year 3 (p<0.0001) • No significant changes in visual acuity from baseline to year 3 (p>0.49)  <i>Previously injected eyes:</i>  • No significant change over 3 years (mobility test: p=0.7398, white light full-field sensitivity: p=0.6709) • No significant changes in visual acuity from baseline to year 3 (p>0.49)

Abbreviations: AAV, adeno-associated virus; ITT, intention-to-treat; LCA, Leber's congenital amaurosis; MLMT, multi-luminance mobility testing; N, number; NCT, National Clinical Trial (ClinicalTrials.gov); SAE, serious adverse events; SD, standard deviation

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