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New Drug Evaluation: Voretigene neparvovec-rzyl intraocular suspension for subretinal injection

Date of Review: March 2018
Generic Name: voretigene neparvovec-rzyl

End Date of Literature Search: 01/10/2018
Brand Name (Manufacturer): Luxturna (Spark Therapeutics)
Dossier Received: Yes

Research Questions:

1. What is the efficacy of voretigene neparvovec compared to placebo or currently available treatments of inherited retinal dystrophy due to retinal pigment epithelium-specific 65 kDa (RPE65) protein mutations?
2. Is voretigene neparvovec safe for treatment of inherited retinal dystrophy due to RPE65 mutations?
3. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with voretigene neparvovec?

Conclusions:

- There is insufficient evidence to determine if voretigene neparvovec has any significant impact on functional status or disease progression. Similarly, there was no difference in visual acuity at 1 year compared to placebo (mean difference [MD] 0.16 logMAR; 95% Confidence Interval [CI] -0.14 to 0.08, p=0.17).[1]
- There is insufficient evidence that voretigene neparvovec improves patient's ability to navigate in low light environments. Mean improvement in MLMT score was 1.6 (95% CI 0.72 to 2.41, p=0.0013) and was maintained up to 2 years.[1] Evidence was downgraded based on high or unclear risk of bias, indirectness with use of a surrogate endpoint and small number of patients studied, and inconsistency based on only a single published phase 3 trial with small treatment effect. Because the MLMT is a relatively new test developed to study voretigene neparvovec, there is insufficient evidence that this change in score correlates with a real-world ability to navigate in low light environments.
- Evaluations of functional vision and visual fields demonstrate similar trends 1 year after treatment. The mean change in the full-field light sensitivity threshold testing (FST) was -2.11 (95% CI -3.19 to -1.04 log10 cd.s/m^2).[1] FST evaluates visual function and uses light flashes at varying intensities to determine the luminance at which the patient is able to perceive light.[2] A change of 1 log measurement is considered by the FDA to be clinically significant.[1]
- Upon evaluation of quality of life using an unvalidated patient questionnaire with a range of 0 to 250 points, there was little impact on patient's perceived quality of life or ability to complete daily tasks (MD of 2.6 to 3.9-point improvement from baseline compared to -0.2 to 0.2-point change in the control group; p=0.001).[1] It is unlikely that this change, which corresponds to a difference of less than 2% on this scale, represents a clinically important difference in daily function or quality of life.
- There is insufficient evidence to evaluate long-term safety of voretigene neparvovec. Ocular adverse events occurred in 66% of patients, and were generally consistent with the type and incidence of adverse events observed after vitrectomy surgery.[2] The most common adverse events included conjunctival hyperemia (22%), cataracts (20%), increased intraocular pressure (15%), retinal tear (10%), macular hole (7%), eye irritation, eye pain, and maculopathy (5% each).[2]

- Serious treatment-related ocular events (endophthalmitis and permanent vision loss) occurred in 2 patients (4.8%) following administration of voretigene neparvovec.[2]
- There is insufficient evidence to evaluate differences in subpopulations, though no differences in efficacy or safety were observed in post-hoc analyses based on age or sex.[2]

Recommendations:
- Recommend implementation of prior authorization criteria to limit use in the population studied (**Appendix 2**).
- The Committee also referred funding of voretigene neparvovec to the Health Evidence Review Commission (HERC) for prioritization consideration.

Background:
In late 2016, the Food and Drug Administration (FDA) approved voretigene neparvovec, the first gene therapy indicated for patients with confirmed biallelic RPE65 mutation-associated hereditary retinal diseases.[3] Inherited retinal diseases are a significant cause of blindness and decreased visual acuity in children and young adults and can be caused by a wide variety of genetic mutations. The RPE65 gene codes for the retinal pigment epithelium-specific 65 kDa (RPE65) protein, a protein responsible for regeneration of light reacting proteins in the retina.[4] Biallelic mutations in RPE65 gene are associated with several conditions including type 2 Leber congenital amaurosis, early onset severe retinal dystrophy, severe early childhood-onset retinal dystrophy, and retinitis pigmentosa type 20.[4] Mutations in the RPE65 gene lead to formation of misfolded or non-functional RPE65 proteins. Without a functional RPE65 protein, retinal cells are unable to convert light to electrical signals resulting in the inability of photoreceptors to respond to light. In addition, patients with RPE65 mutations have progressive degeneration of retinal epithelial cells.[3,4] The exact mechanism of retinal deterioration is unknown, but is thought to be associated with cytotoxic effects resulting from accumulation of nonfunctional RPE65 proteins.[4] Patients with two recessive mutations in the RPE65 gene have progressively decreasing visual acuity. Disease progression is highly variable, poorly characterized in available literature, and the rate and extent of visual loss varies based on the type of mutation. Biallelic mutations are typically associated with significant reduction in visual acuity during childhood (sometimes as early as 6 months of age) through early adulthood.[4] For example, adult patients with Leber congenital amaurosis due to biallelic RPE65 mutations commonly have a visual acuity of less than 20/20,000 and are unable to see hand motion.[4] Patients with early onset severe retinal dystrophy or severe early childhood-onset retinal dystrophy may have milder visual impairment, though all patients with biallelic RPE65 gene mutations typically have impaired visual acuity in low light environments.[4] Visual impairment typically begins with deceased peripheral and night vision (associated with rod photoreceptors) and progresses to involvement of cone photoreceptors which are responsible for color and visual acuity.[4]

The exact incidence of inherited retinal disease associated with biallelic RPE65 mutations is unknown, though estimates from the manufacturer of voretigene neparvovec indicate that biallelic RPE65 mutations occur in 3 to 10 per 1 million patients (corresponding to about 1000 to 3000 current patients in the United States with an estimated 14 to 40 new patients per year).[4,5] Currently, approximately 20 fee-for-service Oregon Health Plan (OHP) patients and 140 patients enrolled in coordinated care organizations have a diagnosis of *unspecified* hereditary retinal dystrophy. It is unclear from claims data how many of these OHP patients may have biallelic RPE65 mutations. Because diagnosis based on clinical symptoms of visual impairment can be difficult, and often different mutations can have a similar clinical presentation, the American Academy of Ophthalmology does recommend genetic testing for patients with inherited retinal diseases.[4,6]

Prior to approval of voretigene neparvovec, there were no pharmacological treatments for inherited retinal diseases. Standard of care included supportive services such as low-vision training and use of visual aid or adaptive mobility devices. The FDA has also approved a device for patients with severe retinitis pigmentosa which induces visual perception in blind patients via electrical stimulation of the retina.[2] Voretigene neparvovec is formulated as an adeno-associated virus vector-based therapy which has been genetically modified to express a normal RPE65 gene.[3] With use of the viral vector, the normal RPE65 gene

is introduced into retinal epithelial cells and has the potential to increase normal RPE65 protein activity in retinal cells and restore the visual cycle.[3] It is administered as a one-time subretinal injection during intraocular surgery. Injections are given in each eye at least 6 days apart with oral corticosteroids started 3 days before the surgery and tapered after the surgery.

Clinically relevant outcomes of interest include improvements in visual acuity, functional vision, and night vision. Increased mobility or independence, greater quality of life, and decreased disease progression are also important outcomes for patients with significant visual impairment.[4] Voretigene neparvovec was approved primarily based on a single phase 3 trial which assessed improvements in mobility evaluated with use of a newly developed tool called the multi-luminance mobility test (MLMT). The MLMT was developed during the course of phase 1 trials and provides a method to quantify changes in mobility performance at various light levels for patients who are visually impaired.[7] Patients were evaluated for the speed and accuracy with which they are able to navigate an obstacle course with both eyes and for each individual eye. The course had 12 different configurations (each standardized for the number of obstacles and turns) which were assigned in a randomized manner in an effort to avoid re-learning upon repetition of the test.[8] The course could be completed at 7 different light levels described in **Table 1,** and was administered from lower to higher light levels.[8] The lowest light level (corresponding to worst visual impairment and the highest MLMT score) at which the patient is able to pass the test was recorded.[1] Passing was defined as the ability to complete the course with fewer than 4 (out of 15 possible) errors and within 3 minutes.[7] Time penalties were also added if the patient went off the course, missed steps in the course, or required redirection.[7] The MLMT was validated with comparison to traditional visual acuity measures, visual function tests, and patient-reported quality of life. The MLMT was able to distinguish between patients with normal vision and those with visual acuity less than 20/63 vision on the Snellen chart.[2,7] Patients with visual acuity better than 20/63 had similar MLMT scores as patients without visual impairment.[7] Correlation of visual acuity in patients with and without visual impairment compared to MLMT scores was good (r^2 of 0.75 to 0.86), but there was weak correlation of MLMT with the degree of visual field (as assessed by the Goldmann test for visual field).[2,7] However, during development of this scale, 71% of tested patients had no change in MLMT score and it is unclear how changes in MLMT may correlate to changes in vision.[7] FDA reviewers considered a MLMT score change of at least 2 to be clinically significant, and a score change of 1 to likely correspond to learning of the course or background fluctuation between groups.[2] FDA reviewers acknowledged that this measure may vary as the difference in illuminance was not consistent between MLMT scores.[2] For example, a change in score from 4 to 6 corresponds to a difference of 9 lux whereas a change in score from 0 to 2 corresponds to a change of 275 lux. Because the MLMT is a relatively new test developed over the course of trials for voretigene neparvovec, it is unclear if an improvement in MLMT score of 2 corresponds to the actual ability of a patient to navigate in low light environments in the real world.

Table 1. Light levels and corresponding environmental description in the Multi-Luminance Mobility Test (MLMT). Light levels were measured at various points throughout the course, and were validated with less than 20% error.[2]

MLMT Score	Illuminance (lux)	Corresponding environment
0	400	Office environment or food court
1	250	Interior of elevator, library or office hallway
2	125	Interior of shopping mall, train or bus at night; 30 min before cloudless sunrise
3	50	Outdoor train station at night or inside of illuminated office building stairwell
4	10	60 minutes after sunset in a city or a bus stop at night
5	4	Cloudless summer night with half-moon or outdoor parking lot at night
6	1	Moonless summer night or indoor nightlight

Visual acuity, a secondary endpoint in this study, was standardized based on logarithm of the minimum angle of resolution (logMAR) scores. A logMAR score of 0.1 corresponds to a change of 5 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, and a change of 0.3 logMAR (15 letters) is commonly accepted as a clinically significant change.[2] Off-chart measurements including counting fingers, identifying hand movement, and light perception, were used if patients were unable to see the largest letters on the chart. Use of the ETDRS scale is often used to evaluate changes in vision; however, because visual impairment for RPE65 mediated retinal dystrophy typically begins with deceased peripheral and night vision, visual acuity may not accurately assess visual impairment in patients with less severe disease. In addition, changes in visual acuity from phase 1 trials were difficult to interpret, and it was not chosen as a primary endpoint for phase 3 trials.[2] In phase 1 trials, 46% of treated eyes had a statistically significant improvement (compared to 16% of untreated eyes), but 16% of treated eyes also had a statistically significant worsening in visual acuity compared to none of the untreated eyes.[2] Full-field light sensitivity threshold testing (FST), another method to assess visual function and night blindness, was also utilized as a secondary endpoint. With FST, light flashes at varying intensities are used to determine the luminance at which the patient is able to perceive light.[2] The minimum clinically important difference for FST has not been established, though values of 10 decibels or 1 log measurement have been suggested as being clinically significant.[1] Exploratory endpoints included quality of life and visual field measurements. Real world quality of life and activities of daily living were assessed using an un-validated, 25-item questionnaire with each question evaluated on a 0 to 10 scale with higher values indicating improved function (total range 0-250 points). The extent of a patient's visual field and peripheral vision was evaluated using the following metrics: Goldmann perimetry and Humphrey computerized testing. Goldmann perimetry is evaluated as the sum total of degrees perceived across 24 meridians with maximum degrees of 1200 to 1400 for non-visually impaired patients.[2] Humphrey testing is evaluated in decibels with higher values indicating improvements in vision. A change of 7 decibels is considered clinically significant.[2]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Voretigene neparvovec was approved primarily on the basis of a single, open-label, crossover, fair quality, phase 3 RCT (n=31) evaluating efficacy and safety in patients with retinal dystrophy associated with confirmed biallelic RPE65 mutations (**Table 3**). The majority of patients enrolled in this trial were white (68%) and female (58%) with an average age of 15 years (range 4-44 years).[1] Patients were required to have a visual acuity worse than 20/60 or visual field less than 20 degrees and sufficient viable retinal cells.[1] The amount of viable retinal cells were assessed using a variety of methods including optical coherence tomography (>100 microns), fundus photography, and clinical exam.[1] FDA reviewers noted that use of only optical coherence tomography to evaluate viable retinal cells may not accurately identify patients with viable retinal cells as 3 of the 20 subjects enrolled based on optical coherence tomography requirements failed to respond to treatment.[2] Therefore, labeling was updated to specify that the patient must have viable retinal cells as determined by the treating physician.[2] Patients were excluded if they had recent intraocular surgery or recent use of high dose vitamin A.[1] Patients were randomized 2:1 to voretigene neparvovec treatment or delayed treatment. Patients in the delayed treatment arm were crossed over to the treatment arm after one year. The primary endpoint was improvement in MLMT from baseline to one year. Secondary endpoints included assessments of visual acuity and assessments of visual function using FST. Other exploratory endpoints included changes in quality of life and other visual changes assessed by Goldmann perimetry or Humphrey computerized testing, contrast sensitivity testing, and pupillary light responses.

Patients in the control group were slightly older (mean age 15.9 years; median 14 years) than treatment group (mean age 14.7 years; median 11 years), and fewer patients randomized to treatment were able to pass the MLMT at 125 lux (with a score of 2) compared to placebo (57% vs. 40% in placebo arm) indicating that patients randomized to treatment had more severe visual impairment compared to control patients.[1] The impact of these differences is unclear, though not unexpected given the small population size. The study was designed as an open label trial due to ethical considerations of performing sham surgery in a mostly

pediatric population. However, this increases risk of performance bias and may bias results in favor of treatment, particularly for subjective outcomes such as quality of life. Risk for reporting bias was unclear. All specified outcomes were reported; however, funding for the study was provided by the manufacturer who was involved in trial design, data analysis, data interpretation, and publication.[1] In addition, the primary endpoint for the trial was changed after input from the FDA and other regulatory agencies. The initial primary endpoint was planned as the sum score of MLMT when evaluated using both eyes, the right eye, and left eye.[2] The primary endpoint was later changed to the MLMT score using both eyes, and scores for individual eyes were reported separately since there was concern that the average value would result in a score which was weighted toward the eye with better vision.

Improvement in MLMT was observed as early as 30 days and was maintained for up to 2 years following treatment. At one year, the mean change from baseline in MLMT score using both eyes was 1.8 (SD 1.1) compared to relatively little change for control patients (0.2; SD 1.0).[1] The mean difference was 1.6 (95% CI 0.72 to 2.41, p=0.0013).[1] Because voretigene neparvovec did not achieve a clinically important difference from the control arm, the FDA relied upon statistical analysis of both mean and median change in MLMT scores.[2,8] The median difference in MLMT score was 2 for patients randomized to voretigene neparvovc (vs. no change with control).[2] FDA reviewers also observed a ceiling effect with use of the MLMT scale which may lead to a systematic underestimation of the treatment effect.[8] For example, patients with a baseline score of 5 could only improve by one MLMT level. There were 4 patients randomized to the treatment arm who had a baseline score of 5 and achieved a maximum change in score of 1, compared to no patients in the control arm.[8] However, levels of 1 lux were chosen as the maximum light level on the MLMT scale because levels below 1 lux were not thought to be pertinent to activities of daily living, and it is unclear if improvement in ability to navigate the MLMT in light levels less than 1 lux has any clinical implications.[7] Similar MLMT scores were also observed with each individual eye.[2,8] Eleven patients (52%) had a change in MLMT score of greater than 2 using both eyes compared to 1 patient (10%) in the control group (MD 42%, NNT 3).[2,3,8] Five of these patients in the treatment arm had a change in MLMT score of 3 and one patient had a MLMT score change of 4.[2,3,8] Results for cross-over control patients were also comparable at 1 year following treatment.[2] Because difference in illuminance was not consistent between MLMT scores, a change in MLMT score of 2 may correspond to a wide range of illuminance levels from 9 lux to 275 lux, and it is unclear if a 2-point score improvement corresponds to the actual ability of a patient to navigate in low light environments in the real world.

Results from FST testing were generally consistent with MLMT evaluations. The mean difference in FST test was -2.11 (95% CI -3.19 to -1.04; p=0.0004) though the clinical significance of this difference is unclear.[1] Similarly, exploratory tests for visual fields demonstrated significant changes with Goldmann perimetry (MD 378.7 degrees; 95% CI 145.5 to 612.0; p=0.006) and Humphrey testing (MD 7.9 decibels, 95% CI 3.5 to 12.2; p<0.001).[2] Mean change in best corrected visual acuity at 1 year was not significantly different between treated patients and placebo (MD 0.16 logMAR corresponding to approximately 8 letters; 95% CI -0.14 to 0.08, p=0.17).[1,2] In a post-hoc analysis of visual acuity, 6 patients (30%) randomized to treatment had a clinically significant improvement in visual acuity (change of 15 or more letters) in the first eye, and 4 patients (20%) had a similar improvement for the second eye.[1] No patients in the control group had a clinically significant improvement in visual acuity.[1] Subgroup analyses based on age or sex demonstrated no differences in efficacy or safety.[2] Results for other subgroups included too few patients to make meaningful conclusions. However, 3 patients randomized to treatment had no improvement in MLMT score for at least one eye. All of these patients were unable to pass the baseline MLMT at the lowest score (400 lux) indicating that patients with advanced disease may not respond to treatment.[8] These patients also had worse visual acuity compared to other treated patients, with baseline visual acuity of 1.6, 1.87, and 2.06 logMAR corresponding to visual acuity less than 20/800.[1]

Despite changes in MLMT, FST and visual fields, there was little change in patient reported quality of life from 30 days to 1 year following treatment. This scale used to assess quality of life has not been validated, but assesses 25 items from 0 to 10 points (total range 0 to 250) with higher scores indicating less difficulty completing daily tasks. The mean improvement at 1 year with treatment was 2.6 to 3.9 points compared to an average change in the control group of -0.2 to 0.2 points (p=0.001). It is unlikely that this change, which corresponds to a difference of less than 2% on this scale, represents a clinically meaningful change in

quality of life. In addition, it is unclear if the effects of voretigene neparvovec will be maintained over time. Results from phase 1 trials of 2 similar formulations of adeno-associated viral vectors for treatment of RPE65 mediated retinal dystrophy indicate that effects of these products gradually decline over time beginning 1 to 3 years after treatment.[2,9] However, data from early phase 1 trials of voretigene neparvovec indicates that the effects of treatment are sustained for 2 to 3 years.[2] The reason for these differences in duration between products is unclear though it may be due to differences in formulation, vector design, or systemic use of perioperative steroids.[2] Long-term data for voretigene neparvovec are not available, and the impact on disease progression is unknown. Long-term follow-up for up to 15 years is planned for patients enrolled in the phase 3 trial.

Clinical Safety:

Safety analysis from the FDA included data from a phase 1 (n=12) and phase 3 trial (n=31).[2] In the phase 1 study, bilateral injections were given to patients in both eyes at intervals of 1.7 to 4.6 years.[2] In the phase 3 study, bilateral injections were only separated by 6 to 18 days. Overall, attrition was low; 2 patients in the phase 3 trial withdrew prior to treatment administration.[1] There were 8 serious adverse events reported in 7 patients; 2 of these events were considered related to treatment (endophthalmitis and permanent vision loss).[2] Ocular adverse events occurred in 66% of patients. Most common ocular events included conjunctival hyperemia or eye redness (22%), cataracts (20%), increased intraocular pressure (15%), retinal tear (10%), macular hole (7%), eye irritation, eye pain, and maculopathy (5%).[2] In addition, FDA labeling advises patients to avoid air travel, travel to high elevations, or scuba diving following administration of voretigene neparvovec.[3] Intraocular air bubbles may form following vitrectomy surgery and changes in altitude may result in expansion of air bubbles and irreversible vision loss. Labeling also recommends providers verify that air bubbles have dissipated by ophthalmic examination prior to engaging in any of these activities.[3] Air bubbles may remain for one week or more following surgery.[3] In general, these adverse reactions are consistent with the type and incidence of adverse events observed after vitrectomy surgery. However, the severity of some of these adverse effects is concerning, and the modest benefit associated with treatment should be weighed against the risks associated with subretinal surgery. Because of the small population enrolled in the clinical trials, the predicted frequency of these adverse effects with real world use is unclear. With administration of systemic steroids before and after surgery, there was no observed immune response to the drug. Post-marketing requirements include ongoing long-term follow-up of patients enrolled in clinical trials for up to 15 years, use of a registry study to evaluate safety in at least 40 patients for up to 5 years after administration, and requirements for pharmacy and surgical training for providers.

Table 2. Pharmacology and Pharmacokinetic Properties.[3]

Parameter	
Mechanism of Action	Genetic mutations in the human RPE65 protein lead to loss of visual function and retinal dystrophy. Voretigene neparvovec is an adeno-associated virus vector-based therapy which has been genetically modified to contain a normal RPE65 gene. With use of the viral vector, the normal RPE65 gene is introduced into retinal epithelial cells and has the potential to increase normal RPE65 protein activity in retinal cells and restore the visual cycle.
Bioavailability	Not applicable
Distribution and Protein Binding	Highest levels of viral vectors occurred in intraocular fluids. Low levels were detected in the optic nerve, optic chiasm, spleen, liver, and occasionally lymph nodes. Vector DNA was present in serum of 10% of patients for up to 3 days post-injection.
Elimination	In approximately 45% of patients, viral vector was present in tears from the injected eye and occasionally from the uninjected eye up to 3 days post-injection. Two patients (7%) had vector DNA in tear samples at 2 weeks after administration.
Half-Life	Not applicable
Metabolism	Not applicable

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Change in visual acuity
2) Change in functional or night vision
3) Quality of life and productivity
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Multi-luminance mobility test (MLMT)

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimen/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Russell, et al.[1] FDA Clinical Review.[2] Phase 3, open label, MC, crossover, RCT	1. Voretigene neparvovec $1.5x10^{11}$ vg (0.3 mL) subretinal injection in each eye 6-18 days apart 2. Delayed treatment; after 1 year, patients were crossed over to treatment arm Randomized 2:1 Prednisone 1 mg/kg/day PO x10 d (max 40 mg/d) beginning 3 days prior to each injection and tapered after surgery	Demographics: - Mean age: 15.1 years (SD 10.9) - Female: 58% - White: 68% - MLMT passing level <125 lux 1. 12 (57%) 2. 4 (40%) Key Inclusion Criteria: - Age ≥3 years - Biallelic RPE65 gene mutations - Visual acuity ≤20/60 or visual field <20 degrees - Sufficient viable retinal cells (retinal thickness by OCT >100 microns within the posterior pole, fundus photography and clinical exam) - Unable to pass MLMT at 1 lux (lowest tested level) but able to pass at higher lux Key Exclusion Criteria: - Use of high dose vitamin A (>3300 IU/ day) or other retinoid	ITT: 1. 21 2. 10 mITT (patients not given treatment excluded) 1. 20 2. 9 Attrition: 1. 1 (5%) 2. 1 (10%)	Primary Endpoint: Mean change from baseline in lux score for the lowest passing level of the MLMT at 1 year 1. 1.8 (SD 1.1) 2. 0.2 (SD 1.0) MD 1.6 (95% CI 0.72 to 2.41); p=0.0013 Secondary Endpoints: Mean white light FST testing with both eyes (mITT; log10 $cd.s/m^2$) 1. -2.08 (SD 0.29) 2. 0.04 (SD 0.44) MD -2.11 (95% CI -3.19 to -1.04); p=0.0004 Mean change from baseline in BCVA 1. 0.16 logMAR (8.1 letters)	NA NA	Serious ocular events: 1. 2 (9.5%) 2. 0 (0%) p-values NR	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. Randomization scheme generated by independent party but concealment of allocation unknown. Randomization stratified by age (<10 or ≥10 years) and baseline MLMT passing level (pass at ≥125 lux or <125 lux). Patients in control group were slightly older (mean age 15.9, median 14 years) than treatment group (mean age 14.7, median 11 years) and a larger percentage of patients with lower MLMT passing level were randomized to treatment (57%) vs. control (40%). Performance Bias: HIGH. Open-label study design. Detection Bias: LOW. Evaluators blinded to treatment group. MLMT evaluated by 2 independent, trained evaluators, with adjudication by a 3rd party if necessary. Data management and statistical analyses conducted by independent party. Attrition Bias: LOW. Attrition low; 1 patient from each group discontinued treatment; ITT analysis performed. One patient in treatment arm was determined to be ineligible after administration (passed MLMT at 1 lux). Reporting Bias: UNCLEAR. Primary outcome changed prior to data analysis in conjunction with FDA. Funding provided by Spark Therapeutics. Sponsors were involved in study design, data analysis, data interpretation, and publication. Two of the primary study investigators disclosed patent ownership for the product, though they have waived any financial interest in the patent. FDA subgroup analysis based on study site was not significantly different from the results of the primary analysis. **Applicability**: Patient: Population not applicable to patients with visual function better than 20/60 or visual field >20 degrees. Patients were required to have sufficient viable retinal cells as assessed by optical coherence tomography and clinical exam. Patients taking recent, vitamin A, tretinoin, isotretinoin, hydroxychloroquine, or other related retino-toxic compounds were excluded.

	Duration: 1 year	or retino-toxic compounds in the past 18 months - Recent intraocular surgery (within 6 months) - Other ocular or systemic conditions which would interfere study interpretation		2. 0.01 logMAR (1.6 letters) MD -0.16 logMAR (95% CI -0.41 to 0.08); p=0.17	NS			Intervention: Standard vitreoretinal techniques for subretinal surgery were used. Efficacy assessed at baseline, 30, 90, 180 and 365 days after 2nd injection (for treatment arm) or randomization (for delayed treatment). Comparator: Delayed treatment appropriate comparator. Use of sham or placebo control was inappropriate due to ethical considerations. Outcomes: MLMT developed over the course of the clinical trials. A change of 2 or more lux levels was considered a clinically meaningful difference. Secondary outcomes support primary analysis though there was no difference in BCVA. Setting: 2 sites in the United States
Abbreviations [alphabetical order]: ARR = absolute risk reduction; BCVA = best corrected visual acuity; cd.s/m^2 = candela seconds per square meter; CI = confidence interval; FST = full-field light sensitivity threshold; ITT = intention to treat; IU = international units; logMAR = logarithm of the minimum angle of resolution; MC = multicenter; MD = mean difference; mITT = modified intention to treat; MLMT – multi-luminance mobility test; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; OCT = optical coherence tomography; PP = per protocol; RCT = randomized controlled trial; SD = standard deviation; vg = vector genomes								

References:

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LUXTURNA safely and effectively. See full prescribing information for LUXTURNA.

LUXTURNA (voretigene neparvovec-rzyl) intraocular suspension for subretinal injection

Initial U.S. Approval: YYYY

----------INDICATIONS AND USAGE----------

LUXTURNA is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s). (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended dose of LUXTURNA for each eye is 1.5×10^{11} vector genomes (vg), administered by subretinal injection in a total volume of 0.3 mL. (2.1)
- Perform subretinal administration of LUXTURNA to each eye on separate days within a close interval, but no fewer than 6 days apart. (2.1)
- Recommend systemic oral 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. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

LUXTURNA is a suspension for subretinal injection, supplied in a 0.5 mL extractable volume in a single-dose 2 mL vial for a single administration in one eye. The supplied concentration (5×10^{12} vg/mL) requires a 1:10 dilution prior to administration. The Diluent is supplied in two single-use 2-mL vials. (3)

----------CONTRAINDICATIONS----------

None.

----------WARNINGS AND PRECAUTIONS----------

- Endophthalmitis: Use proper aseptic injection technique and monitor for signs and symptoms of infection. (5.1)
- Permanent decline in visual acuity: Monitor for visual disturbances. (5.2)
- Retinal abnormalities: Monitor for macular abnormalities, retinal tears or breaks. Do not inject in the immediate vicinity of the fovea. (5.3)
- Increased intraocular pressure: Monitor and manage intraocular pressure elevations. (5.4)
- Expansion of intraocular air bubbles: Air travel and/or scuba diving is not recommended until any intraocular air bubbles have been absorbed. (5.5)
- Cataract: Subretinal injection of LUXTURNA may result in cataract formation or increase in the rate of cataract progression. (5.6)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence $\geq$ 5%) in the clinical trials were 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). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Spark Therapeutics, Inc. at 1-855-SPARKTX, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

Pediatric use: Use in infants under 12 months of age is not recommended because of potential dilution or loss of LUXTURNA after administration due to the active retinal cells proliferation occurring in this age group. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Voretigene neparvovec

Goal(s):

- Restrict use of voretigene neparvovec to patients with retinal dystrophy associated with biallelic RPE65 mutations

Length of Authorization:

Up to 6 months

Requires PA:

- Voretigene neparvovec (applies to both physician administered and pharmacy claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is the request from a provider at a center of excellence who is trained for and following administration and treatment protocols for voretigene neparvovec?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the patient greater than 1 year of age?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient been previously enrolled in clinical trials of gene therapy for retinal dystrophy RPE65 mutations or been previously been treated with gene therapy for retinal dystrophy in the eye(s) receiving treatment?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6

Approval Criteria		
6. Does the patient have other pre-existing eye conditions or complicating systemic diseases that would eventually lead to irreversible vision loss and prevent the patient from receiving full benefit from treatment (eg. severe diabetic retinopathy)?	**Yes**: Pass to RPh. Deny; medical appropriateness	**No:** Go to #7
7. Does the patient have retinal dystrophy with confirmed biallelic RPE65 mutations?	**Yes:** Go to #8 Document genetic testing	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have a visual acuity of at least 20/800 OR have remaining light perception in the eye(s) receiving treatment?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Does the patient have visual acuity of less than 20/60 OR a visual field of less than 20 degrees?	**Yes:** Go to #10 Document baseline visual function	**No:** Pass to RPh. Deny; medical appropriateness
10. Does the provider document presence of neural retina and a retinal thickness >100 microns within the posterior pole as assessed by optical coherence tomography with AND have sufficient viable retinal cells as assessed by the treating physician?	**Yes:** Approve up to 2 doses for up to 6 months. Document retinal thickness and physician attestation	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 3/18 (SS)
Implementation: TBD