

Subject: Gene Therapy for Ocular Conditions
Document #: MED.00120
Status: Reviewed

Publish Date: 04/10/2024
Last Review Date: 02/15/2024

Description/Scope

This document addresses the use of gene therapy to treat inherited ophthalmic disease. Therapy can involve the supplementation of a defective gene or the introduction of a factor to decrease disease progression. Currently, only voretigene neparvovec-rzyl (Luxturna[®], Spark Therapeutics, Philadelphia, PA), a gene replacement therapy intended to treat retinal dystrophies caused by biallelic RPE65 gene mutations, has been approved by the FDA.

Position Statement

Medically Necessary:

The use of voretigene neparvovec-rzyl is considered **medically necessary** in individuals who meet *all* of the following criteria:

- A. A diagnosis of retinal dystrophy due to confirmed *RPE65* mutation(s) in *both* alleles; **and**
- B. At least 1 year of age; **and**
- C. For each eye indicated for treatment, sufficient viable retinal cells as determined by non-invasive means, such as optical coherence tomography (OCT) and/or ophthalmoscopy as evidenced by *one* of the following:
 - 1. An area of retina within the posterior pole of greater than 100 μ m thickness shown on OCT; **or**
 - 2. Three or more disc areas of retina without atrophy or pigmentary degeneration within the posterior pole; **or**
 - 3. Remaining visual field within 30 degrees of fixation as measured by a III4e isopter or equivalent;**and**
- D. For each eye indicated for treatment, have not had intraocular surgery within 6 months.

Note: Voretigene neparvovec-rzyl has not been adequately studied or in individuals who are pregnant or unwilling to use contraception for 4 months after treatment.

Investigational and Not Medically Necessary:

The use of voretigene neparvovec-rzyl is considered **investigational and not medically necessary** when the above criteria are not met.

Repeat injections of voretigene neparvovec-rzyl in the same eye are considered **investigational and not medically necessary** in all cases.

The use of all other gene replacement therapies to treat any ocular condition is considered **investigational and not medically necessary**.

Rationale

Voretigene neparvovec-rzyl

On December 19, 2017 the U.S. Food and Drug Administration (FDA) approved voretigene neparvovec-rzyl (Luxturna), the first gene replacement (MAF) therapy approved in the U.S. to treat an inherited disease. Voretigene neparvovec-rzyl is an adeno-associated virus vector-based gene therapy for the treatment of biallelic RPE65 mutation-associated retinal dystrophy. Voretigene neparvovec-rzyl is supplied in single dose vials to be used in a single eye and is administered via subretinal injection. Treatment must be done separately in each eye on separate days, with at least 6 days between procedures. Use of this therapy is limited to those with evidence of viable retinal cells and to those age 12 months or older. Infants younger than 12 months of age are undergoing active retinal cell proliferation and there is a potential for dilution or loss of voretigene neparvovec-rzyl after administration in this population.

FDA approval of voretigene neparvovec-rzyl was primarily based on the results of an open-label, randomised, controlled phase 3 trial (Russell, 2017). A total of 29 individuals aged 3 years or older with Leber congenital amaurosis type 2 (LCA2) due to confirmed biallelic *RPE65* gene mutations with both eyes with a visual acuity of 20/60 or worse or visual field less than 20 degrees in any meridian or both, and sufficient viable retinal cells present in each eye participated in the study. The intervention group received a subretinal injection of voretigene neparvovec-rzyl in the poorer-seeing eye, followed by an injection into the second eye 6-18 days after the initial injection. A control group of 9 individuals did not receive therapy for 1 year at which time they could cross over and receive recombinant adeno-associated virus voretigene neparvovec-rzyl therapy (AAV2-hRPE65v2). The primary efficacy endpoint was the change from baseline to 1 year in the score of the multi-luminance mobility testing (MLMT), an assessment of functional vision at specified light levels. Secondary efficacy endpoints also included full-field light sensitivity threshold (FST) testing and best-corrected visual acuity (BCVA), each averaged over both eyes. At 1 year, the mean bilateral MLMT score improvement in the intervention group was 1.8 (standard deviation [SD] 1.1) compared to 0.2 (SD 1.0) in the control group for a difference of 1.6 (95% confidence interval [CI], 0.72-2.41, p=0.0013). Mean FST scores in the intervention group improved by 30 days following intervention and remained stable at 1 year. There was no meaningful change in FST scores in the control group at 1 year. The BCVA scores in the intervention group did show an insignificant numerical improvement over the control group. The authors noted this was not unexpected as BCVA is a measure of foveal, cone-mediated function, and the *RPE65* gene mutations result in a rod-mediated disease. The most common treatment-related ocular adverse events included elevated intraocular pressure, cataract and eye inflammation and were considered mild or moderate. There were no reported serious product-related adverse events or harmful immune responses. One individual in the intervention group did experience loss of visual acuity in the first eye which was significant based upon the VA measurement criteria, however, the individual did not report a change in vision. The authors noted the loss might be due to foveal thinning following subretinal injection, however, the analysis was inconclusive.

In an open label phase 1-2 trial, the safety and efficacy of gene therapy with a recombinant adeno-associated virus 2/2 (rAAV2/2) vector carrying the *RPE65* complementary DNA was evaluated for 3 years following treatment (Bainbridge, 2015). A total of 12

children and young adults (6 to 23 years old) with early-onset, severe retinal dystrophy, caused by mutations in *RPE65*, were treated with RPE65 gene supplementation. Individuals received treatment in one eye; 4 individuals received a lower dose while the remaining 8 individuals received a higher dose. In addition to a baseline evaluation, individuals underwent interval evaluations for 3 years, measuring visual acuity, contrast sensitivity, color vision, and spectral sensitivities. While there was a greater proportion of individuals with improved retinal sensitivity among those treated with higher versus lower doses, due to the widely differing level of improvement among the individuals and the small number of participants, a dose-response effect may be present but not definitively concluded. Additionally, treatment benefits did not appear to be lasting. Retinal sensitivity improvement was reported within 1 to 2 months following therapy with progressive improvement continuing for 6 to 12 months. Following 12 months, retinal sensitivity declined in the majority of cases, although 2 individuals showed a continued improvement over pre-intervention levels over 3 years. Visual acuity was improved in 1 individual who showed a similar improvement in the contralateral untreated eye. The authors noted rAAV2/2 vector carrying the *RPE65* cDNA gene therapy led to a "temporary, variable and incomplete restoration of retinal function in humans."

Bennett and colleagues (2016) assessed the safety and efficacy of administering the treatments in the contralateral eye in a follow-up to the initial study. A total of 11 of the 12 original participants received an injection in the contralateral, untreated eye and were evaluated on a regular basis for 3 years. An individual with glaucoma in the uninjected eye could not be included in this follow-up study. One individual developed bacterial endophthalmitis following the injection. The remaining adverse effects related to the procedure included dellen formation (n=2) and cataracts (n=1), all of which were successfully treated. For the majority of outcomes, results for the second injected eye were compared with results over the same follow-up period for the initial injected eye. In a pooled analysis, results from full-field light sensitivity threshold testing showed robust improvements in both rod and cone function in the contralateral eyes by day 30 through year 3. A pooled analysis also did not show any significant changes in visual acuity from baseline through year 3 in either eye. There were reported significant improvements in mobility testing and pupillary light reflex testing results which lasted through year 3.

Weleber and associates (2016) treated 12 individuals in a small, non-randomized multi-center clinical trial. A total of 8 adults and 4 children with either LCA or severe early-childhood-onset retinal degeneration (SECORD) with varying degrees of visual acuity were included in the study. Individuals received a subretinal injection containing either 1.8×10^{11} (group 1) or 6×10^{11} (group 2) vector genomes of rAAV2-CBhRPE65. While 9 of the 12 individuals showed an improvement in at least 1 measure of visual function, the specific area and amount of improvement varied among individuals. Two individuals reported a decrease in BCVA or visual field area that was greater in the treated eye compared to the untreated eye. Adverse events related to the study agent included ocular hyperemia (n=2) and photopsia (n=1). The authors noted that larger studies with longer follow-up is needed to further assess side effects or safety concerns.

Le Meur and colleagues (2018) evaluated the efficacy and tolerance of injections of AAV serotypes 2 and 4 (AAV2/4) RPE65 in an RPE65 gene deficiency LCA in a phase 1/2 study. A total of 9 individuals aged 9 to 42 years with 2 confirmed RPE65 gene mutations were grouped into 3 cohorts based upon age and injected viral vector dose. Cohort 1 consisted of adults who received the lowest dose of viral vector, cohorts 2 and 3 received higher doses of viral vector. Each participant received 2 to 5 simultaneous unilateral subretinal injections with dosages between 1.22×10^{10} to 4.8×10^{10} vector genomes (vg) into the eye with the greatest visual impairment. All 9 individuals were followed for 1 year and 6 of the individuals agreed to additional follow-up for 2 to 3.5 years. Visual acuity loss progression varied among the cohorts. In cohorts 1 and 3, there were no observed alterations in visual acuity. Cohort 2 showed a trend towards improved visual acuity. Visual acuity in the treated eye remained stable during the follow-up period. Visual acuity in the untreated eye trended toward reduced visual acuity. However, none of the alterations attained statistical significance. Individuals who presented with nystagmus and intermediate initial visual acuity reported the most marked improvements (cohort 2), while individuals in cohort 3 with correct initial visual acuity without nystagmus showed less of an improvement. The authors postulated that this may be related to the clinical modification in nystagmus. Changes in mobility, evaluated using travel time through a maze under different lighting conditions, were not significantly changed from pre-injection through 1 year follow-up. The injections were well tolerated with only transient symptoms reported. An analysis of the mean retinal thickness at 1-, 2-, or 3-year follow-up revealed no alterations in retinal thickness in the treated or untreated eyes. The authors noted that the possibility of retinal thinning may occur and anticipate assessing this factor in further follow-up.

Le Meur and associates compared their current study to previous studies. The researchers increased the number of injection subretinal sites (2-5) compared to earlier studies in an attempt to increase the contact between the viral vector and the retinal surface, but it remains unclear whether this approach provided additional benefit. In addition, the dose increments in this study were smaller than those in previous trials (1.22×10^{10} to 4.8×10^{10} versus 1.5×10^{10} vg to 6.11×10^{11} vg, respectively). The authors noted that the dose used may not have been sufficient to achieve a meaningful response or to prevent further deterioration. The authors concluded that long term follow-up is needed to evaluate the persistence of the effects and evaluate the treatment effect on retinal degeneration.

Maguire and colleagues (2019) reported on the durability of results of individuals participating in earlier dose dependent phase 1 and phase 3 trials. The results included the 4-year follow-up data from a phase 1 study and the 2-year follow-up data from a phase 3 study. The common endpoints included the MLMT performance change within the illuminance range evaluated, FST testing, and BCVA. At year 4, phase 1 individuals who received the same dosage as those individuals in the phase 3 study showed improvements in tests of functional vision and in visual function which were consistent with those in phase 3 study. The authors note that maximal or near maximal effects appear to be observed by day 30 with the gains maintained in year 4. In addition, the authors noted that the safety profile is consistent with vitrectomy and subretinal injection. The study did not include any individuals less than 4 years of age.

Treatment with voretigene neparvovec-rzyl is limited to individuals at least 1 year old. The Luxturna package insert (PI) label includes information regarding use in the pediatric population:

Treatment with LUXTURNA is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during cell proliferation.

Early studies have shown safety and variable efficacy with variable duration for up to 4 years following injection therapy (Cideciyan, 2008; Le Meur, 2018; Jacobson, 2012; Maguire, 2009; Maguire, 2021; Testa, 2013). There appears to be a limited or no systemic immune response to the subretinal AAV2 vector delivery (Jacobson, 2012). There remain several unknowns related to gene therapy, including which individuals would benefit from therapy and the most efficacious delivery method. Ongoing durability remains a concern (Bennett, 2016; Le Meur, 2017; Webeler, 2016). Progressive perfoveal chorioretinal atrophy has been reported in individuals undergoing voretigene neparvovec-rzyl therapy, although visual acuity improved or remained stable in the majority of individuals (Gange, 2022). At the current time, the safety and efficacy of repeat injections into the same eye have not been evaluated in clinical studies.

Other gene therapies

Clinical trials evaluating the use of gene therapy for other ocular conditions are ongoing. In a randomized phase 2 trial, Fischer and colleagues (2019) evaluated the safety and efficacy of subretinal injections of a functional version of the choroideremia (*CHM*) gene in 6 men with molecularly confirmed CHM. Among the 6 participants, gene therapy with an adeno-associated virus vector designed to

deliver a functional version of the *CHM* gene was associated with maintenance or improvement of visual acuity over 2 years, although the difference was not significant from control eyes. A number of unknowns remain, including optimal age of treatment (including stage of disease progression), adverse events such as iatrogenic retinal detachment from the procedure (1 out of 6 participants in the study developed iatrogenic retinal detachment from the procedure), and optimal patient selection, including whether certain genetic mutations result in better treatment outcomes. A phase 3 trial (STAR trial) is currently underway to further assess gene therapy to treat those with CHM (NCT03496012). This trial evaluating the use of timrepigene emparvovec (BIIB111/AAV2-REP1) will follow individuals for 12 months after treatment.

In a phase I/II trial, Cehajic-Kapetanovic and associates (2020) reported on the 6-month results of young men with X-linked retinitis pigmentosa who were treated with gene therapy. The trial population consisted of 3 cohorts (n=6 each) who were treated with varying concentrations of adeno-associated viral vector encoding codon-optimized human RPGR (AAV8.coRPGR). The primary outcome was safety; visual acuity was evaluated as a secondary outcome. The study did not show any dose limiting toxicities and did suggest the potential for reversal of visual field loss. Although the early results are promising, this data represent only initial results; additional studies are needed. The use of gene therapy to treat RPGR mutations represents an additional challenge as the gene coding sequence is unstable. The RPGR sequence instability and the lack of understanding about its function could lead to the production of a nonfunctional or deleterious protein for the human retina (Martinez-Fernandez De La Camara, 2020).

The results of early phase 1/2 trials suggest that gene therapy may benefit several ocular diseases, however further research is needed to further evaluate safety and efficacy as well as to define the characteristics of those who will benefit from therapy (Dimopoulos, 2018; Lam, 2019; MacLaren, 2014; Parker, 2014; von Krusenstiern, 2023; Xue, 2018). Phase 3 trials have also been published, but no gene therapies have been FDA approved with the exception of voretigene neparvovec-rzyl (Biossee, 2021; Newman, 2021). Studies evaluating the use of gene therapy to treat non-inherited ocular disease, such as age-related macular degeneration are also underway.

Background/Overview

Hereditary retinal dystrophies or inherited retinal diseases (IRDs) are progressive disorders which typically result in blindness at a young age. There are approximately 220-260 mutations associated with IRDs including the *RPE65* mutation (Martinez-Fernandez De La Camara, 2020; Russell, 2017). Missense mutations in the retinal pigment epithelium-specific protein 65 kDa (RPE65) result in a more severe form of the retinal degenerative disease that is associated with photoreceptor dysfunction and degeneration (Cideciyan, 2013). A lack of functional RPE65 results in rod photoreceptor cells that are unable to respond to light, contributing to decreased ability to see in low light conditions and diminished visual fields. As retinal degeneration progresses and affects cones, the disorder leads to blindness (FDA, 2017).

More than 25 genes have been associated with LCA; there is no treatment for the majority of these genotypes (Gange, 2022). IRDs attributed to biallelic RPE65 mutations are associated with the subtypes of LCA type 2 and retinitis pigmentosa (RP) type 20. In the United States (U.S.) there are an estimated 1000 to 3000 individuals with biallelic RPE65 mutation-associated retinal dystrophy (FDA, 2017). Individuals with LCA caused by RPE65 retain a largely normal outer retinal structure as compared to the amount of visual loss, a unique characteristic which makes potentially restoring vision via gene replacement therapy viable (Wright, 2015). However, gene replacement therapy has been shown to provide a partial improvement in visual dysfunction, as evidenced by improved vision, but does not appear to slow photoreceptor degeneration. Prior to the development of gene therapy, there were no pharmacologic treatments available to treat IRDs.

The 2016 American Academy of Ophthalmology (AAO) recommends genetic testing be ordered at the initial visit for individuals with a suspected inherited retinal degenerative disease. The causative mutation can be identified in up to 60-80% of affected individuals, which can guide treatment decisions. The scope of genetic testing recommended varies, multi-gene testing may be necessary when there are multiple causative genes, while single gene analysis might be more appropriate for certain conditions. For diseases such as LCA, which is caused by multiple different genes, it can be more efficient to order a single test which has been designed to specifically evaluate for all of the known causative genes (Stone, 2012). A listing of the genes causing retinal disease can be accessed here: <https://sph.uth.edu/retnet/>.

In 2019, an attempt to standardize the detection and reporting of disease-causing variants across the genome, the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen) published technical standards for interpreting and reporting constitutional copy-number variants (CNVs). The ACMG created 5 variant classification categories which are scored based on an evidence scoring metric: pathogenic, likely pathogenic, uncertain significance, likely benign and benign. This framework establishes a means to clinically interpret sequence variants in terms of a gene-disease relationship. The authors note:

Understanding the validity of a gene-disease association is the first step in selecting appropriate genes to be tested in a clinical setting. Clinical utility of gene sequencing decreases as the evidence for a disease association decreases. Laboratories are responsible for evaluating how the strength of evidence for gene-disease correlation may limit their ability to classify variants as pathogenic or likely pathogenic.

The eye has several unique features which make it a good model for gene therapy. The blood retinal barrier allows for the introduction of antigens without eliciting an inflammatory immune response, known as ocular immune privilege. Treatment is likely to result in long-term or lifetime results, due to the non-dividing nature of photoreceptors or retinal pigment epithelium cells. The small size of structures requires only a small amount of therapeutics to be administered. Visualization can be accomplished using several techniques due to the inherent optical clarity of the eyeball. Also, as many disease processes have a degree of symmetry, one eye can serve as a control for comparison while treating the contralateral eye (Jolly, 2019).

Agents used to deliver gene therapy can be administered by either subretinal or intravitreal injections. Subretinal injections allow for a more precise delivery of the agent into the retinal pigment epithelium (RPE) and photoreceptor area. However, subretinal injections are more invasive and the placement of the subretinal bleb can lead to macular holes and retinal detachment. Intravitreal injections are considered better for targeting the inner retina but are more likely to generate an immunological response as there is the possibility of a wider systemic spread of the agent (Ziccardi, 2019).

Treatment with voretigene neparvovec-rzyl involves the use of a standard three-port pars plana vitrectomy with removal of the posterior cortical vitreous followed by an injection of the vector genome of adeno-associated virus 2 (AAV2).hRPE65v2 into the subretinal space, creating a localized dome-shaped retinal detachment. The localized retinal detachment typically resolves within 14 to 24 hours following surgery. Minimal persistent subretinal fluid at the macula typically resolves within 2 to 3 days.

Warnings and Precautions

Warnings from the FDA PI Label (2022) include the following:

- Endophthalmitis: Use proper aseptic injection technique and monitor for signs and symptoms of infection.

- Permanent decline in visual acuity: Monitor for visual disturbances.
- Retinal abnormalities: Monitor for macular abnormalities, retinal tears or breaks and chorioretinal atrophy. Do not inject in the immediate vicinity of the fovea.
- Increased intraocular pressure: Monitor and manage intraocular pressure elevations.
- Expansion of intraocular air bubbles: Air travel and/or scuba diving is not recommended until any intraocular air bubbles have been absorbed.
- Cataract: Subretinal injection of Luxturna may result in cataract formation or increase in the rate of cataract progression.

In addition, the PI label includes the following language regarding 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).

Definitions

Biallelic Mutation: A mutation in both copies of a particular gene that affects the function of both copies.

Gene replacement therapy: A medical treatment that introduces or alters genetic material to replace the function of a missing or dysfunctional gene with the goal of lessening or eliminating a disease process that results from genetic dysfunction.

Mutation: A change in the usual DNA sequence of a particular gene; the change can be harmful, beneficial or neutral.

Retina: Light sensitive tissue located at the back of the eye which transmits images along the optic nerve to the brain.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT
0810T Subretinal injection of a pharmacologic agent, including vitrectomy and 1 or more retinotomies

HCPCS
J3398 Injection, voretigene neparvovec-rzyl, 1 billion vector genomes [Luxturna]

ICD-10 Diagnosis
H35.50-H35.54 Hereditary retinal dystrophy

When services are Investigational and Not Medically Necessary:

For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

When services are also Investigational and Not Medically Necessary:

HCPCS
J3490 Unclassified drugs [when specified as a gene therapy agent other than voretigene neparvovec-rzyl (Luxturna)]

ICD-10 Diagnosis
All diagnoses

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SPK-RPE65
timrepigene emparvovec

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	02/15/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale and References sections.
	12/28/2023	Updated Coding section with 01/01/2024 HCPCS changes to remove C9770 deleted as of 01/01/2024; also added CPT 0810T.
Revised	02/16/2023	MPTAC review. Revised Note in position statement to remove gender specific term and minor correction in use of the number 4 of four months. Updated Rationale and References sections.
Reviewed	02/17/2022	MPTAC review. Updated Rationale and References sections.
Reviewed	02/11/2021	MPTAC review. Updated Rationale and References sections.
	12/16/2020	Updated Coding section with 01/01/2021 HCPCS changes; added C9770.
Revised	02/20/2020	MPTAC review. Revised title of document from "Voretigene neparvovec rzyt (Luxturna)" to "Gene Therapy for Ocular Conditions". Added investigational and not medically necessary statement for all other types of gene therapy treatment. Removed redundant "gene therapy" language. Updated Description, Rationale, Background, Coding, References and Websites for Additional Information sections.
Reviewed	03/21/2019	MPTAC review. Revised title from TM to [®] symbol. Updated References.
	12/27/2018	Updated Coding section with 01/01/2019 HCPCS changes; added J3398, removed C9032 deleted 12/31/2018.
	06/28/2018	Updated Coding section with 07/01/2018 HCPCS changes; added C9032. Updated Rationale to include information regarding pediatric population.
New	03/22/2018	MPTAC review. Initial document development.

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