Policy Number	**RX501.098**
Policy Effective Date	**08/01/2026**

Gene Therapy for Inherited Retinal Dystrophy

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of care developed by: nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated, and coverage is not required for non-formulary drugs.

Coverage

Voretigene neparvovec-rzyl (Luxturna), an adeno-associated virus vector-based gene therapy administered via subretinal injection **may be considered medically necessary** for individuals with vision loss due to biallelic *RPE65* variant-associated retinal dystrophy if they meet **ALL** the following criteria:

- Are adults (age < 65 years) or children (age ≥ 12 months).
- Documentation of the following:
  - Genetic testing confirming presence of biallelic *RPE65* pathogenic variant(s) or likely pathogenic variants (see Policy Guidelines for additional details):
    - Single *RPE65* pathogenic variant or likely pathogenic variant found in the homozygous state.
    - Two *RPE65* pathogenic variants or likely pathogenic variants found in the *trans* configuration (compound heterozygous state) by segregation analysis.
- Presence of viable retinal cells as determined by treating physicians as assessed by optical coherence tomography imaging and/or ophthalmoscopy:
  - An area of retina within the posterior pole of >100 µm thickness shown on optical coherence tomography; OR
  - ≥ 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole; OR
  - Remaining visual field within 30° of fixation as measured by III4e isopter or equivalent.
- Individual has not previously received *RPE65* gene therapy in the intended eye.

Other applications of voretigene neparvovec-rzyl **are considered experimental, investigational, and/or unproven**.

Policy Guidelines

The recommended dose of voretigene neparvovec-rzyl for each eye is 1.5×10^{11} vector genomes (vg), administered by subretinal injection in a total volume of 0.3 mL.

Subretinal administration of voretigene neparvovec-rzyl to each eye must be performed on separate days within a close interval, but no fewer than 6 days apart.

Systemic oral corticosteroids equivalent to prednisone at 1 mg/kg/d (maximum, 40 mg/d) are recommended for a total of 7 days (starting 3 days before administration of voretigene neparvovec-rzyl to each eye) and followed by a tapering dose during the next 10 days.

Voretigene neparvovec-rzyl should be administered in the surgical suite under controlled aseptic conditions by a surgeon experienced in performing intraocular surgery.

Voretigene neparvovec-rzyl is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and voretigene neparvovec-rzyl would potentially be diluted or lost during cell proliferation.

Diagnosis of Biallelic RPE65-Mediated Inherited Retinal Dystrophies
Genetic testing is required to detect the presence of pathogenic or likely pathogenic variants in the *RPE65* gene in individuals with documented vision loss. By definition, pathogenic or likely pathogenic variant(s) must be present in both copies of the *RPE65* gene to establish a diagnosis of biallelic *RPE65*-mediated inherited retinal dystrophy.

A single *RPE65* pathogenic or likely pathogenic variant found in the homozygous state (e.g., the presence of the same pathogenic or likely pathogenic variant in both copies of the *RPE65* gene) establishes a diagnosis of biallelic *RPE65*-mediated dystrophinopathy.

However, if 2 different *RPE65* pathogenic or likely pathogenic variants are detected (e.g., compound heterozygous state), confirmatory testing such as segregation analysis by family studies may be required to determine the *trans* versus *cis* configuration (e.g., whether the 2 different pathogenic or likely pathogenic variants are found in different copies or in the same copy of the *RPE65* gene). The presence of 2 different *RPE65* pathogenic or likely pathogenic variants in separate copies of the *RPE65* gene (*trans* configuration) establishes a diagnosis of biallelic *RPE65*-mediated dystrophinopathy. The presence of 2 different *RPE65* pathogenic or likely pathogenic variants in only 1 copy of the *RPE65* gene (*cis* configuration) is not considered a biallelic *RPE65*-mediated dystrophinopathy.

Next-generation sequencing and Sanger sequencing typically cannot resolve the phase (e.g., *trans* vs. *cis* configuration) when 2 *RPE65* pathogenic or likely pathogenic variants are detected. In this scenario, additional documentation of the *trans* configuration is required to establish a diagnosis of biallelic *RPE65*-mediated inherited retinal dystrophy. Table PG1 provides a visual representation of the genetic status requirements to establish a diagnosis of *RPE65*-mediated inherited retinal dystrophy.

Table PG1. Genetic Diagnosis of *RPE65*-Mediated Inherited Retinal Dystrophy

Genetic Status	Diagram	Diagnosis of *RPE65*-Mediated Inherited Retinal Dystrophy?
Homozygous	*RPE65* gene copy #1 (- - - - - - X - - - - - -) *RPE65* gene copy #2 (- - - - - - X - - - - - -) X=single *RPE65* pathogenic or likely pathogenic variant	Yes

Heterozygous (*trans* configuration)	*RPE65* gene copy #1 (- - - - - - X - - - - - -) *RPE65* gene copy #2 (- - - O - - - - - - - - -) X=*RPE65* pathogenic or likely pathogenic variant #1 O=*RPE65* pathogenic or likely pathogenic variant #2	Yes
Heterozygous (*cis* configuration)	*RPE65* gene copy #1 (- - O - - X - - - - - -) *RPE65* gene copy #2 (- - - - - - - - - - - - -) X=*RPE65* pathogenic or likely pathogenic variant #1 O=*RPE65* pathogenic or likely pathogenic variant #2	No

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG2). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the recommended standard terminology - "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" - to describe variants identified that cause Mendelian disorders.

Table PG2. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

DNA: deoxyribonucleic acid

Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence

Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequency with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology. DNA: deoxyribonucleic acid

Genetic Counseling

Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Description

Inherited retinal dystrophy can be caused by recessive variants in the *RPE65* gene. Individuals with biallelic variants have difficulty seeing in dim light and experience progressive loss of vision. These disorders are rare and have traditionally been considered untreatable. Gene therapy with an adeno-associated virus vector expressing *RPE65* has been proposed as a treatment to improve visual function.

Inherited Retinal Dystrophies

Inherited retinal dystrophies are a diverse group of disorders with overlapping phenotypes characterized by progressive degeneration and dysfunction of the retina. (1) The most common subgroup is retinitis pigmentosa (RP), which is characterized by a loss of retinal photoreceptors, both cones and rods. (1, 2) The hallmark of the condition is night blindness (nyctalopia) and loss of peripheral vision. These losses lead to difficulties in performing visually dependent activities of daily living such as orientation and navigation in dimly lit areas. Visual acuity may be maintained longer than peripheral vision, though eventually, most individuals progress to vision loss.

RPE65 Gene

RP and Leber congenital amaurosis (LCA) both have subtypes related to pathogenic variants in *RPE65*. The *RPE65* (retinal pigment epithelium-specific protein 65-kD) gene encodes the RPE65 protein, which is an all-trans-retinal isomerase, a key enzyme expressed in the retinal pigment epithelium (RPE) that is responsible for regeneration of 11-*cis*-retinol in the visual cycle. (3) The *RPE65* gene is located on the short (p) arm of chromosome 1 at position 31.3

(1p31.3). Individuals with biallelic variations in *RPE65* lack the RPE65 enzyme; this lack leads to build-up of toxic precursors and damage to RPE cells, loss of photoreceptors, and eventually complete blindness. (4)

Epidemiology

RPE65-associated inherited retinal dystrophy is rare. The prevalence of LCA has been estimated to be between 1 in 33,000 and 1 in 81,000 individuals in the United States. (5, 6) LCA subtype 2 (*RPE65*-associated LCA) accounts for between 5% and 16% of cases of LCA. (5, 7-9) The prevalence of RP in the United States is approximately 1 in 4000 (2) with approximately 1% of patients with RP having *RPE65* variants. (10) Table 1 summarizes the estimated pooled prevalence of *RPE*-associated inherited retinal dystrophy and the range of estimated cases based on the estimated 2017 United States population.

Table 1. Estimated Pooled Prevalence of *RPE65*-Associated Inherited Retinal Dystrophy and Estimated Number of Patients

Description	Low	High
Estimated pooled prevalence of *RPE65*-mediated inherited retinal dystrophies (e.g., LCA type 2, *RPE65*-mediated RP)	1:330,000	1:130,000
Estimated number of patients	1,000	2,500

LCA type 2: Leber congenital amaurosis type 2; RP: retinitis pigmentosa.

Gene Therapy

Gene therapies are treatments that change the expression of genes to treat disease, for example, by replacing or inactivating a gene that is not functioning properly or by introducing a new gene. Genes may be introduced into human cells through a vector, usually a virus. Adeno-associated viruses (AAV) are frequently used due to their unique biology and simple structure. These viruses are in the parvovirus family and are dependent on coinfection with other viruses, usually adenoviruses, to replicate. AAVs are poorly immunogenic compared with other viruses but can still trigger an immune response making it a challenge to deliver an effective dose without triggering an immune response that might render the gene therapy ineffective or harm the patient. (4) There are over 100 different AAVs, and 12 serotypes have been identified so far, labeled AAV1 to AAV12; of these, AAV2, AAV5, and AAV8 have been most extensively studied in ocular gene therapies. (11) The recombinant AAV2 is the most commonly used AAV serotype in gene therapy. (12)

The eye is a particularly appropriate target for gene therapy due to the immune privilege provided by the blood-ocular barrier and the minimal amount of vector needed, given the size of the organ. Gene therapy for *RPE65* variant-associated retinal dystrophy using various AAV vectors to transfect cells with a functioning copy of *RPE65* in the RPE cells has been investigated.

Regulatory Status

On December 19, 2017, the AAV2 gene therapy vector voretigene neparvovec-rzyl (Luxturna™; Spark Therapeutics) was approved by the U.S. Food and Drug Administration for use in patients

with vision loss due to confirmed biallelic *RPE65* variant-associated retinal dystrophy. (13) Spark Therapeutics received breakthrough therapy designation, rare pediatric disease designation, and orphan drug designation.

Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. Randomized control trials (RCTs) are preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Gene Therapy for *RPE65* Variant-Associated Retinal Dystrophy

Clinical Context and Therapy Purpose

The purpose of gene therapy in individuals who have retinal dystrophies caused by *RPE65* variants is to restore the visual cycle so that vision is improved and individuals can function more independently in their daily activities.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with biallelic *RPE65* variant-associated retinal dystrophy who have vision loss. Individuals must still have sufficient, viable retinal cells to respond to the missing protein and restore visual function.

Interventions

The treatment being considered is gene augmentation therapy.

Voretigene neparvovec-rzyl (Luxturna) is an U.S. Food and Drug Administration (FDA) approved adeno-associated viral serotype 2 (AAV2) gene therapy vector that supplies a functional copy of the *RPE65* gene within retinal pigment epithelium (RPE) cells.

Comparators
There are no other FDA-approved pharmacologic treatments for *RPE65* variant-associated retinal dystrophy. Supportive care such as correction of refractive error and visual aids and assistive devices may aid in performing daily activities.

Outcomes
Outcomes related to both how the eyes function and how an individual functions in vision-related activities of daily living are important for evaluating the efficacy of gene therapy for the treatment of retinal dystrophy. Relevant outcomes measures are listed in Table 2 below.

Table 2. Health Outcome Measures Relevant to Retinal Dystrophy

Outcome	Measure (Units)	Description	Clinically Meaningful Difference (If Known)
Functional vision	Multi-Luminance Mobility Testing (score change)	Measures ability to navigate at different levels of environmental illumination; scores at a specific time range from 0 (minimum) to 6 (maximum). Positive change indicates improved ability to navigate under different lighting conditions	1 light level (14)
Light sensitivity	Full-field Light Sensitivity Threshold (log10 [cd.s/m^2])	Measures light sensitivity of the entire retina; more negative values indicate improved sensitivity to light	10 dB or 1 log (14)
Visual acuity	ETDRS test charts (logMAR)	Measures central visual function; 0.1 logMAR = 5 ETDRS letters or 1 line; lower logMAR signifies better visual acuity	10-15 ETDRS letters (1-2 lines) (15, 16)
Visual field	Humphrey Visual Field (dB)	Measures area in which objects can be detected in the periphery of the visual environment, while the eye is focused on a central point; Humphrey measures static fields; higher dB indicates increased sensitivity	3-dB change (17)

	Goldmann perimetry (sum total degrees)	Measures kinetic fields; higher sum total degrees indicates a larger field of vision.	
Contrast sensitivity	Pelli-Robson Contrast Sensitivity Charts (log contrast sensitivity)	Measures ability to see objects of different saturations (shades of gray); larger log contrast sensitivity indicates letters of lower contrast can be read correctly	
Visual-specific ADL(s)	NEI VFQ-25 (sum)	Measures patient report of effect of visual function on activities of daily living for individuals with poor vision; higher scores indicate visually dependent tasks are perceived to be less difficult.	2- to 4-point change (18, 19)

ADL: activities of daily living; dB: decibel; ETDRS: Early Treatment of Diabetic Retinopathy Study; log10 (cd.s/m^2): logarithm of candela second per meter squared; logMAR: logarithm of the minimum angle of resolution; NEI: National Eye Institute; VFQ: Visual Function Questionnaire.

Because the hallmark of the disease is nyctalopia, the manufacturer developed a novel outcome measure that assesses functional vision by evaluating the effects of illumination on speed and accuracy of navigation. The measure incorporates features of visual acuity (VA), visual field (VF), and light sensitivity. The Multi-Luminance Mobility Test (MLMT) grades individuals navigating a marked path while avoiding obstacles through various courses at 7 standardized levels of illumination, ranging from 1 to 400 lux (see examples in Table 3). Graders monitoring the navigation assign each course either a "pass" or "fail" score, depending on whether the individual navigates the course within 180 seconds with 3 or fewer errors. The lowest light level passed corresponds to an MLMT lux score, which ranges from 0 (400 lux) to 6 (1 lux). The score change is the difference between the MLMT lux score in year 1 and baseline. A positive score change corresponds to passing the MLMT at a lower light level. The reliability and content validity of the MLMT were evaluated in 60 (29 normal sighted, 31 visually impaired) individuals who navigated MLMT courses 3 times over 1 year. (20)

Table 3. Light Levels for Multi-Luminance Mobility Test (21)

Light Levels (lux)	Example of Light Level in Environment
1	Moonless summer night; indoor nightlight
4	Cloudless night with half-moon; parking lot at night
10	1 hour after sunset in city; bus stop at night
50	Outdoor train station at night; inside of lighted stairwell
125	30 minutes before sunrise; interior of train or bus at night
250	Interior of elevator or office hallway
400	Office environment or food court

Improvements in vision and function over a period of a year would demonstrate treatment efficacy. Evidence of durability of these effects over a period of several years or more is also needed given the progressive nature of the disease process.

Study Selection Criteria

In addition to the PICO selection criteria, additional selection criteria for studies to assess a therapy are listed below:

- To assess efficacy outcomes, seek comparative controlled prospective trials, with preference for randomized controlled trials.
- In the absence of such trials, seek comparative observational studies, with preference for prospective studies.
- To assess longer term outcomes and adverse effects, also seek single-arm studies that capture longer periods of follow up and/or larger populations.
- Consistent with the 'best available evidence approach', within each category of study design, prefer larger sample size studies and longer duration studies.
- Seek to exclude studies with duplicative or overlapping populations.

Systematic Reviews

Britten-Jones et al. (2022) published a systematic review that summarized gene therapies for monogenic retinal and optic nerve diseases. (22) A total of 151 reports on gene therapies for 16 different genetic variants were included, of which 54 reports concerned gene therapies using AAV-based vectors targeting the *RPE65* variant. Seven of the 54 reports were published clinical trials: 1 phase 3 RCT by Russell et al. (2017) (14) and 6 single-arm, open-label, phase 1/2 trials in which the untreated eye served as the comparator. (23-28) These trials are all summarized in the following sections. Statistically significant improvements were found in 2 major outcomes, full-field stimulus threshold (FST) test and mobility evaluation assessed using MLMT. Five of the 7 published trials reported adverse events; the most common adverse events were ocular hypertension/increase in intraocular pressure (16 of 79 patients), ocular pain/discomfort (12 of 79 patients), and the development or worsening of cataracts (7 of 79 patients). The systematic review by Wang et al. (2020), summarized below, was also included in the review. (29) Due to significant heterogeneity in the included studies, a pooled meta-analysis was not performed; rather, a visual summary of the outcomes of different trials was presented.

Tuohy et al. (2021) conducted a systematic review and meta-analysis that assessed the efficacy of gene therapies for inherited retinal degenerations. (30) Six studies on AAV2-mediated gene therapy in patients with *RPE65*-associated Leber congenital amaurosis (LCA) were included, by Jacobson et al. (2012), Testa et al. (2013), Bainbridge et al. (2015), Weleber et al. (2016), Russell et al. (2017), and Le Meur et al. (2018); these studies are all summarized in the following sections. (14, 23, 24, 27, 28, 31) FST showed significant improvements with red light (risk ratio [RR], 1.89, treated vs. untreated eye; p=.04) and blue light (RR, 2.01, treated vs. untreated eye; p=.001). Modest (although not statistically significant) improvements were found in VA (weighted mean difference [WMD], -0.06 logMAR improvement over treated vs. untreated eye; 95% confidence interval [CI], -0.14 to 0.02; p=.16), ambulatory navigation/mobility (RR, 1.35; 95% CI, 0.78 to 2.35; p=.29), and central retinal thickness (RR, 1.15; 95% CI, 0.45 to 3.00; p=.77). Limitations of the meta-analysis included insufficient number of RCTs (only 1 available) and variability in vector design/amount delivered across trials.

Wang et al. (2020) also conducted a systematic review that assessed the association between changes in visual function and application of gene therapy in patients with *RPE65*-associated LCA. (29) The same 6 studies included in the systematic review by Tuohy et al. (2021) were included in this study. A significant improvement in change in VA in the treated eye relative to the untreated eye was found at 1 year (-0.10 logMAR; 95% CI, -0.17 to -0.04; p=.002), but not at 2 to 3 years (WMD, 0.01; 95% CI, -0.00 to 0.02; p=.15) after treatment. At 1 year after treatment, FST sensitivity to blue flashes also improved by 1.60 log (95% CI, 0.66 to 2.55; p=.0009); however, the difference was not statistically significant for red flashes (WMD, 0.86; 95% CI, -0.29 to 2.01; p=.14). Central retinal thickness was, on average, 19.21 µm lower in treated eyes than in untreated eyes (95% CI, -34.22 to -4.20; p=.01) at 2 to 3 years after treatment.

Subsection Summary: Systematic Reviews

A recent systematic review (N=151 total records) summarized efficacy and safety outcomes from studies on gene therapies for monogenic diseases of the retina and optic nerve. For *RPE65*-mediated retinal dystrophies, gene therapy showed statistically significant improvements in FST and MLMT, while the most common adverse events were ocular hypertension/increase in intraocular pressure, ocular discomfort/pain, and the development or worsening of cataracts. Another systematic review found an improvement in FST, but not in VA, mobility, or central retinal thickness, with gene therapy treatment for *RPE65*-associated LCA. A third systematic review found that *RPE65*-gene therapy for LCA is associated with an improvement of VA and FST in up to 2 years after treatment. Most studies included in these 3 systematic reviews were nonrandomized studies in which the untreated eye served as the comparator.

Randomized Controlled Trials

One gene therapy (voretigene neparvovec) for patients with biallelic *RPE65* variant-associated retinal dystrophy has RCT evidence. The pivotal RCT, titled "The efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with *RPE65*-mediated inherited retinal dystrophy" (NCT00999609), was an open-label trial of patients ages 3 or older with biallelic *RPE65* variants, VA worse than 20/60, and/or a VF less than 20^{o} in any meridian, with sufficient viable retinal cells. (14) Patients meeting these criteria were randomized 2:1 to intervention (n=21) or control (n=10). The trial was conducted at a children's hospital and university medical center. Patients were enrolled between 2012 and 2013. The intervention treatment group received sequential injections of 1.5E11 vg AAV2-hRPE65v2 (voretigene neparvovec) to each eye no more than 18 days apart (target, 12 days; standard deviation [SD], 6 days). The injections were delivered in a total subretinal volume of 0.3 mL under general anesthesia. The control treatment group received voretigene neparvovec 1 year after the baseline evaluation. Patients received prednisone 1 mg/kg/d (max, 40 mg/d) for 7 days starting 3 days before injection in the first eye and tapered until 3 days before injection of the second eye, at which point the steroid regimen was repeated. During the first year, follow-up visits occurred at 30, 90, and 180 days, and 1 year. Extended follow-up is planned for 15 years. The efficacy outcomes were compared at 1 year. The primary outcome was the difference in mean bilateral MLMT score change. MLMT graders were masked to treatment group. The trial was

powered to have greater than 90% power to detect a difference of 1 light level in the MLMT score at a 2-sided type I error rate of 5%. Secondary outcomes were hierarchically ranked: 1) difference in change in FST testing averaged over both eyes for white light; 2) difference in change in monocular (first eye) MLMT score change; 3) difference in change in VA averaged over both eyes. Patient-reported vision-related activities of daily living using a Visual Function Questionnaire (VFQ), and VF testing (Humphrey and Goldmann) were also reported. The VFQ has not been validated.

At baseline, the mean age was about 15 years (range, 4 to 44 years) and approximately 42% of the participants were male. The MLMT passing level differed between the groups at baseline; about 60% passed at less than 125 lux in the intervention group versus 40% in the control group. The mean baseline VA was not reported but appears to have been between approximately 20/200 and 20/250 based on a figure in the manufacturer briefing document. One patient in each treatment group withdrew before the year 1 visit; neither received voretigene neparvovec. The remaining 20 patients in the intervention treatment and 9 patients in the control treatment groups completed the year 1 study visit. The intention-to-treat (ITT) population included all randomized patients.

The efficacy outcome results at year 1 for the ITT population are shown in Table 4. In summary, the differences in change in MLMT and FST scores were statistically significant. No patients in the intervention group had worsening MLMT scores at 1 year compared with 3 patients in the control group. Almost two-thirds of participants in the intervention arm showed maximal improvement in MLMT scores (passing at 1 lux) while no participants in the control arm were able to do so. Significant improvements were also observed in Goldmann III4e and Humphrey static perimetry macular threshold VF exams. The difference in change in VA was not statistically significant although the changes correspond to an improvement of about 8 letters in the intervention group and a loss of 1 letter in the control group. The original VA analysis used the Holladay method to assign values to off-chart results. Using, instead, the Lange method for off-chart results, the treatment effect estimate was similar, but variability estimates were reduced (difference in change, 7.4 letters; 95% CI, 0.1 to 14.6 letters). No patients in the control group experienced a gain of 15 or more letters (≤0.3 logMAR) at year 1, while 6 of 20 patients in the intervention group gained 15 or more letters in the first eye and 4 patients also experienced this improvement in the second eye. Contrast sensitivity data were collected but were not reported.

Table 4. Efficacy Outcomes Results at Year 1 in the Pivotal Phase 3 Trial of Gene Therapy for *RPE65* Variant-Associated Retinal Dystrophy

Outcomes	Intervention Mean (SD)	Control Mean (SD)	Difference (95% CI)	p
Primary outcome				
Bilateral MLMT change score	1.8 (1.1)	0.2 (1.0)	1.6 (0.72 to 2.41)	0.001
Secondary outcomes				

Bilateral FST change, log10 (cd.s/m^2)	-2.08 (0.29)	0.04 (0.44)	-2.11 (-3.19 to 1.04)	0.000
First eye MLMT change score	1.9 (1.2)	0.2 (0.6)	1.7 (0.89 to 2.52)	0.001
Bilateral VA change, logMAR	-0.16 (SD NR)[a]	0.01 (SD NR)[b]	-016 (-0.41 to 0.08)	0.17
Other supportive outcomes				
Goldman VF III4e change (sum total degrees)	302.1 (289.6)	-76.7 (258.7)	378.7 (145.5 to 612.0)	0.006
Humphrey VF, foveal sensitivity change, dB	2.4 (9.7)	2.3 (5.3)	0.04 (-7.1 to 7.2)	0.18
Humphrey VF, macula threshold change, dB	7.7 (6.2)	-.02 (1.7)	7.9 (3.5 to 12.2)	0.001
Visual Function Questionnaire, subject	2.6 (1.8)	.01 (1.4)	2.4 (1.0 to 3.8)	0.001

CI: confidence interval; dB: decibel; FST: full-field light sensitivity threshold; MLMT: Multi-Luminance Mobility Test; NR: not reported; SD: standard deviation; VA: visual acuity; VF: visual field.

[a] Corresponds to mean improvement of about 8 letters (i.e., »1.5 lines).

[b] Corresponds to mean loss of about 1 letter.

The manufacturer briefing document reports results out to 2 years of follow-up. (32) In the intervention group, both functional vision and visual function improvements were observed for at least 2 years. At year 1, all 9 control patients received bilateral injections of voretigene neparvovec. After receiving treatment, the control group experienced improvement in MLMT (change score, 2.1; SD, 1.6) and FST (change, -2.86; SD, 1.49). VA in the control group improved an average of 4.5 letters between years 1 and 2. Overall, 72% (21/29) of all treated patients achieved the maximum possible MLMT improvement at 1 year following injection.

Two patients (1 in each group) experienced serious adverse events; both were unrelated to study participation. The most common ocular adverse events in the 20 patients treated with voretigene neparvovec were mild to moderate: elevated intraocular pressure, 4 (20%) patients; cataract, 3 (15%) patients; retinal tear, 2 (10%) patients; and eye inflammation, 2 (10%) patients. Several ocular adverse events occurred only in 1 patient each: conjunctival cyst, conjunctivitis, eye irritation, eye pain, eye pruritus, eye swelling, foreign body sensation, iritis, macular hold, maculopathy, pseudopapilledema, and retinal hemorrhage. One patient experienced a loss of VA (2.05 logMAR) in the first eye injected with voretigene neparvovec; the eye was profoundly impaired at 1.95 logMAR (approximately 20/1783 on a Snellen chart) at baseline.

Maguire et al. (2019) published the results of the open-label follow-on phase 1 study at year 4 and the phase 3 study at year 2. (26) Mean (SD) MLMT lux score change was 2.4 (1.3) at 4 years compared with 2.6 (1.6) at 1 year after administration in phase 1 follow-on subjects (n=8). Mean (SD) MLMT lux score change was 1.9 (1.0) at 2 years and 1.9 (1.0) at 1-year post-administration in the original intervention group (n=20). The mean (SD) MLMT lux score change

was 2.1 (1.6) at 1-year post-administration in control subjects (n=9). Therefore, durability for up to 4 years has been reported, with observation ongoing.

In 2021, Maguire et al. published phase 3 trial results at 3 and 4 years. (33) Mean (SD) MLMT score change at year 4 for patients who received the original intervention (n=21) was 1.7 (1.1) compared to 1.8 (1.0) at year 3. For patients who received delayed intervention after serving as controls for year 1 (n=10), mean (SD) MLMT score change at year 3 was 2.4 (1.5). Therefore, durability of treatment for up to 4 years continues to be reported, with observation ongoing. Overall, 71% of patients with a year 3 visit were able to pass MLMT at the lowest light level. One patient in the original intervention group experienced retinal detachment at year 4.

Subsection Summary: Randomized Controlled Trials

In the pivotal RCT, patients in the voretigene neparvovec group demonstrated greater improvements on the MLMT, which measures the ability to navigate in dim lighting conditions, compared with patients in the control group. The difference in mean improvement was both statistically significant and larger than the *a priori* defined clinically meaningful difference. Most other measures of visual function were also significantly improved in the voretigene neparvovec group compared with the control group, except VA. Improvements seemed durable over a period of 2 years. The adverse events were mostly mild to moderate; however, 1 patient lost 2.05 logMAR in the first eye treated with voretigene neparvovec by the 1-year visit. There are limitations in the evidence. There is limited follow-up available. Therefore, long-term efficacy and safety are unknown. The primary outcome measure has not been used previously in RCTs and has limited data to support its use. Only the MLMT assessors were blinded to treatment assignment, which could have introduced biased assessment of other outcomes. The modified VFQ is not validated, so effects on quality of life remain uncertain. Durability of treatment with respect to MLMT change score has been observed for up to 4 years.

Early Phase Trials

Based on preclinical studies performed in animals, early phase studies of gene augmentation therapy for *RPE65*-associated LCA were initiated in 2007 by several independent groups of investigators. The initial reports of the results of these studies began to be published in 2008. The studies did not have an untreated control group, but several used a patient's untreated eye as a control. Characteristics of the studies are shown in Table 5. Most cohorts included in the studies have been followed in several publications. The baseline visual function, gene constructs, vector formulations, and surgical approaches used by different investigators have varied. Voretigene neparvovec was administered to the Children's Hospital of Pennsylvania cohort.

Table 5. Characteristics of Phase 1/2 studies of Gene Therapy for *RPE65* Variant-Associated Retinal Dystrophy

Cohort (Registration)	Author (Year)	Country (Institution)	Participant	Treatment	Follow-Up
Voretigene neparvovec-rzyl					

CHOP (NCT00516477, NCT01208389)	Maguire (2008) (34); Maguire (2009) (25); Simonelli (2010) (35); Ashtari (2011) (36); Bennett (2012) (37); Testa (2013) (31); Ashtari (2015) (38); Bennett (2016) (39); Ashtari (2017) (40)	U.S./Children's Hospital of Pennsylvania	• N=12 • Age range, 8-44 y • *RPE65*-associated LCA	• Vector: AAV2-hRPE65v2 • Administration: subretinal space of worse seeing eye • Vector dose: 1.5E10 to 1.5E11 vg • Volume delivered: 0.15 mL • Systemic steroids: Yes • Contralateral eye treated with 1.5E11 vg during follow-up study	Up to 3 y
Other Gene Therapies					
London (NCT00643747)	Bainbridge (2008) (41); Stieger (2010) (42); Bainbridge (2015) (27); Ripamonti (2015) (43).	U.K./Moorfield's Eye Hospital; University College London	• N=12 • Age range, 6-23 y • Early-onset, *RPE65*-associated severe retinal dystrophy	• Biological: tgAAG76 • Vector: rAAV2/2-hRPE65p-hRPE65 • Administration: subretinal space of worse seeing eye • Vector dose: 1E11 • Volume delivered: 1.0 mL • Systemic steroids: Yes	Up to 3 y
Scheie/Shands (NCT00481546)	Hauswirth (2008) (44); Cideciyan (2008) (45); Cideciyan (2009) (46, 47); Jacobson (2012) (24);	U.S./Scheie Eye Institute of the University of Pennsylvania; Shands Children's Hospital, University of Florida	• N=15 • Age range, 10-36 y • *RPE65*-associated LCA	• Vector: rAAV2-CBSB-hRPE65 • Administration: subretinal space of worse seeing eye • Vector dose: 5.96E10 to 18E10	Up to 6 y

	Cideciyan (2013) (48); Cideciyan (2014) (49); Jacobson (2015) (50)			• Volume delivered: 0.15-0.30 mL • Systemic steroids: No	
Israel (NCT00821340)	Banin (2010) (51)	Israel/Hadassah-Hebrew University Medical Center	N=10	• Vector*:* rAAV2-CB-hRPE65 • Administration: subretinal space of worse seeing eye • Vector dose: 1.19E10 • Volume delivered: 0.3 mL • Systemic steroids: No	3 y
Casey/UMass (NCT00749957)	Weleber (2016) (28, 52)	U.S./Casey Eye Institute, Oregon Health & Science University; University of Massachusetts	• N=12 • Age range, 6-39 y • RPE65-associated LCA or SECORD	• Vector: rAAV2-CB-hRPE*65* • Administration: subretinal space of worse seeing eye • Vector dose: 1.8E11 to 6E11 • Volume delivered: 0.45 mL • Systemic steroids: No	Up to 5 y
Nantes (NCT01496040)	Le Meur (2018) (23)	France/Nantes University Hospital	• N=9 • Age range, 9-42 y • RPE65-associated LCA	• Vector: rAAV2/4-hRPE65 • Administration: subretinal space of worse seeing eye • Vector dose: 1.2E10 to 4.8E10 • Volume delivered: 0.20-0.80 mL • Systemic steroids: Yes	Up to 3.5 y

NCT03252847	Michaelides et al. (2024) (53)	U.S. and UK	• N=45 • Age range, 11-61 • RPGR-XLRP	• Vector: AAV5-hRKp.RPGR • Administration: Subretinal injection • Vector dose: 3 dose levels (1.0 × 10^{11} vg/ml; 2.0 × 10^{11} vg/ml; 4.0 × 10^{11} vg/ml) • Volume delivered: range, 0.10 to 0.80 mL • Systemic steroids: Yes	Up to 52 weeks
NCT03316560	Yang et al. (2025) (54)	Duke Eye Center/ Cincinnati Eye Institute/Oregon Health and Science University/Retina Foundation of the Southwest	• N=29 • Age range, 15-55 • RPGR-XLRP	• Vector: AAV2tYF-GRK1-RPGR • Administration: subretinal injection • Vector dose: 5 dose levels (2.48 × 10^{10} vg/eye; 7.45 × 10^{10} vg/eye; 2.24 × 10^{11} vg/eye; 6.8 × 10^{11} vg/eye [maximum tolerated dose]; 1.99 × 10^{12} vg/eye [highest dose; not continued]) • Volume delivered: up to 0.3 mL • Systemic steroids: Yes	Up to 24 months

AAV: adeno-associated viruses; CHOP: Children's Hospital of Pennsylvania; LCA: Leber congenital amaurosis; ML: milliliters; NCT: national clinical trial; RPGR: retinitis pigmentosa GTPase regulator;

SECORD: severe early-childhood onset retinal degeneration; U.S.: United States; U.K.: United Kingdom; VA: visual acuity; vg: vector genomes; XLRP: X-linked retinitis pigmentosa; y: year(s).

Voretigene Neparvovec - CHOP Cohort

Several publications have described various outcomes and subgroups of the cohort included in the phase 1/2 studies of voretigene neparvovec. (25, 31, 34-40) Early results showed improvement in subjective and objective measurements of vision (i.e., dark adaptometry, pupillometry, electroretinography, nystagmus, ambulatory behavior). (25, 35, 36) Although the samples were too small for subgroups analyses, the investigators noted that the greatest improvement appeared to be in children. Three-year follow-up of 5 of the first injected eyes (in patients from Italy) was reported. (31) There was a statistically significant improvement in VA between baseline and 3 years ($p<.001$). All patients maintained increased VF and a reduction of the nystagmus frequency compared with baseline. Three-year follow-up is also available for both the originally injected eye and contralateral eye in 11 patients. (39) Statistically significant improvements in mean mobility and full-field light sensitivity persisted to year 3. The changes in VA were not significant. Ocular adverse events were mostly mild (Dellen formation in 3 patients and cataracts in 2 patients). One patient developed bacterial endophthalmitis.

Long-term follow-up for safety was reported in the manufacturer's Food and Drug Administration(FDA) briefing documents. (55) This follow-up included the 12 patients in the phase 1 study as well as the 29 patients in the phase 3 study. Two, phase 2 patients had 9 years of follow-up, 8 patients had 8 years of follow-up, and all 12 patients had at least 7 years of follow-up. Four, phase 3 patients had 4 years of follow-up, and the remaining patients had between 2 and 3 years of follow-up. No deaths occurred. The adverse events tended to occur early and diminish and resolve over time. While all patients experienced at least 1 adverse event, 85% of the adverse events reported were of mild or moderate intensity. Fourteen serious adverse events were reported by 9 patients, but none were assessed as related to the product; 1 was assessed as related to the administration procedure (retinal disorder) and another as related to a periocular steroid injection (increased intraocular pressure). Ocular adverse events that were assessed as related to treatment, required clinical management or impacted the benefit-risk profile occurred in 81 eyes (41 patients): macular disorders (9 eyes, 7 patients), increased intraocular pressure (10 eyes, 8 patients), retinal tear (4 eyes, 4 patients), infections/inflammation (5 eyes, 3 patients), and cataracts (16 eyes, 9 patients). Nine eyes in 7 patients had a 15-letter or more loss in VA. Four of the eyes had VA loss within a month of surgery, and the other 5 eyes had VA loss at or after the first year. No deleterious immune responses were observed in any patients.

Fischer et al. (2024) published follow-up results from the PERCEIVE trial, an ongoing, post-authorization, prospective, multicenter observational study. (56) A total of 103 patients were treated with voretigene neparvovec and followed for a maximum of 2.3 years (median, 0.8 years). A total of 34% of the patients experienced ocular treatment-emergent adverse events which were most commonly chorioretinal atrophy. Intraocular inflammation and/or procedure related infection occurred in 7 patients. VA changes from baseline were not clinically

significant. Mean changes from baseline in full-field light-sensitivity threshold testing (white light) at 1 month, 6 months, 1 year, and 2 years were -16.59 dB (51 eyes), -18.24 dB (42 eyes), -15.84 dB (10 eyes), and -13.67 dB (13 eyes), respectively.

Other Gene Therapies - London Cohort

At least 4 publications following the London cohort are available. (27, 41-43) Preliminary results showed increased retinal sensitivity in 1 of 3 participants. After 3 years of follow-up in all 12 patients, 2 patients had substantial improvements (10 to 100 times as high) in rod sensitivity that peaked around 12 months after treatment and then declined. There was no consistent improvement overall in VA. A decline in VA of 15 letters or more occurred in 2 patients. Intraocular inflammation and/or immune responses occurred in 5 of the 8 patients who received the higher dose and in 1 of 4 patients who received the lower dose. The immune response was deleterious in 1 patient.

Scheie/Shands Cohort

Results for patients in the Scheie/Shands cohort have also been reported in many publications. (24, 44-50) Visual function was reported to have improved in all patients. Dark-adapted FST showed highly significant increases from baseline in the treated eye and no change in the control eye. Cone and rod sensitivities improved significantly in the treated regions of the retina at 3 months, and these improvements were sustained through 3 years. Small improvements in VA were reported, and the improvement appeared to be largest in eyes with the lowest baseline acuities. Retinal detachment and persistent choroidal effusions were reported in 1 patient each; both were related to surgery. However, at a mean follow-up of 4.6 years, the investigators noted that while improvements in vision were maintained overall, the photoreceptors showed progressive degeneration. In 3 patients followed for 5 to 6 years, improvements in vision appeared to peak between 1 and 3 years after which there was a decline in the area of improved sensitivity in all 3 patients.

Israel Cohort

Although the registration for this study indicates that 10 patients were enrolled and followed for 3 years, only the short-term results of 1 patient have been reported. (51) In that patient, there was an increase in vision as early as 15 days after treatment.

Casey/UMass Cohort

Two publications have reported results for the Casey/UMass cohort. (28, 52) In 9 of 12 patients, there was improvement in 1 or more measures of visual function. VA increased in 5 patients, 30° VF hill of vision increased in 6 patients, total VF hill of vision increased in 5 patients, and kinetic VF area increased in 3 patients. The improvements persisted to 2 years in most patients. National Eye Institute VFQ-25 scores improved in 11 of 12 patients. Subconjunctival hemorrhage occurred in 8 patients, and ocular hyperemia occurred in 5 patients.

Results at 5 years following treatment were available for 11 of 12 patients, with 1 patient lost to follow-up. (52) Improvements in VA and static perimetry persisted during years 3 to 5 in all 4 pediatric patients, with no consistent changes in kinetic perimetry. In 2 of these patients, VA in

the untreated eye also improved in years 3 to 5. Most adult subjects had no consistent changes in VA or static perimetry. In 4 of 5 adult subjects with poor baseline VA, progressive loss of vision in 1 or both eyes was noted during years 3 to 5. No significant adverse safety events were observed with results, providing further evidence that treatment at an early age promotes improved outcomes.

Nantes Cohort
One publication has described results of the Nantes cohort. (23) In 8 of 9 patients, there was an improvement in VA of more than 2.5 letters at 1 year after injection; improvements were greatest for patients with a baseline VA between 7 and 31 letters and those with nystagmus. After 2 years of follow-up, the surface area of the VF had increased in 6 patients, decreased in 2 patients, and was the same in 1 patient. For the 6 patients with 3 years of follow-up, 4 continued to have improvements in VF.

U.S./U.K. Cohorts
Michaelides et al. (2024) published a phase 1/2 study evaluating the safety and efficacy of subretinal AAV5-hRKp.RPGR gene therapy via subretinal injection in males with RPGR-associated X-linked retinitis pigmentosa (XLRP) at 5 sites in the U.S. and U.K. (53) This open-label, multicenter trial included dose escalation, dose confirmation, and randomized controlled dose expansion phases. Participants were aged ≥5 years and had confirmed RPGR pathogenic variants. A total of 49 participants were enrolled: 10 in dose escalation, 3 pediatric in dose confirmation, and 36 in dose expansion randomized 1:1:1 to low dose, intermediate dose, or deferred control; 45 received treatment. Follow up was 52 weeks for treated participants and 26 weeks for controls. No dose-limiting events occurred. Two serious adverse events (retinal detachment, uveitis) and one outside the reporting period (increased intraocular pressure) were reported; ocular inflammation occurred in 55.6% of treated participants but was mitigated by corticosteroid prophylaxis. At week 26, improvements favored treatment: vision-guided mobility least square (LS) mean difference at 1 lux -36.96 s (95% CI, -68.10 to 5.82; p=.022), static perimetry LS mean difference 1.96 dB (95% CI, 0.59 to 3.34; p=.006), microperimetry LS mean difference 1.06 dB (95% CI, 0.05 to 2.07; p=.041), and BCVA LS mean difference 3.39 letters (95% CI, 0.22 to 6.56; p=.037). Improvements persisted at week 52 in treated eyes.

Duke Eye Center/Cincinnati Eye Institute/Oregon Health and Science University/Retina Foundation of the Southwest
Yang et al. (2025) reported preliminary results from HORIZON, an ongoing 5-year, Phase 1/2, open-label, multicenter dose-escalation study evaluating a recombinant adeno-associated viral (rAAV2tYF) vector delivering AGTC-501, a functional full-length *RPGR* gene, via subretinal injection. (54) The study enrolled 29 male participants with a confirmed diagnosis of XLRP at 4 centers in the United States. AGTC-501 was administered sequentially across 5 dose levels in 6 groups, with each eligible participant receiving treatment in 1 eye. All participants experienced ≥1 treatment-emergent adverse event (TEAE), and 11 (38%) experienced ≥1 grade 3 TEAE. Six participants (21%) experienced ≥1 ocular serious adverse event considered related to AGTC-501, including retinal detachment (n=4), subcapsular cataract (n=1), and glaucoma (n=1).

Preliminary evidence of efficacy was observed at the maximum tolerated dose. At 24 months, 11 eyes showed a gain of 5 to 15 ETDRS letters, and 3 showed a gain of fewer than 5 letters. Four eyes had a loss of ≤5 letters, 1 eye had a loss of 5 to 10 letters, and 1 eye experienced a loss of more than 15 letters.

Subsection Summary: Early Phase Trials

Voretigene neparvovec appears to have durable effects to at least 4 years in a small number of patients with follow-up. Other gene therapies tested in early phase trials have shown improvements in retinal function but variable durability of effect; some patients from 2 cohorts who initially experienced improvements have subsequently experienced declines after 1 to 3 years. Adverse events of gene therapy tended to occur early; most were mild to moderate and diminished over time. Seven of 41 patients treated with voretigene neparvovec have had a loss of 15 letters or more in at least 1 eye. Most studies have reported minimal immune response.

Summary of Evidence

For individuals who have vision loss due to biallelic *RPE65* variant-associated retinal dystrophy who receive gene therapy, the evidence includes systematic reviews, randomized controlled trials (RCTs), and uncontrolled trials. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Biallelic *RPE65* variant-associated retinal dystrophy is a rare condition. It is recognized that there will be particular challenges in generating evidence for this condition, including recruitment for adequately powered RCTs, validation of novel outcome measures, and obtaining longer-term data on safety and durability. While gene therapy with voretigene neparvovec is approved by the U.S. Food and Drug Administration (FDA), there are no other approved pharmacologic treatments for this condition. A recent systematic review found statistically significant improvements in full-field stimulus threshold test (FST) and Multi-Luminance Mobility Test (MLMT) from gene therapy for *RPE65*-mediated retinal dystrophies; the most common adverse events included ocular hypertension/intraocular pressure increase and ocular pain/discomfort. Another systematic review on gene therapy for *RPE65*-associated Leber congenital amaurosis (LCA) found an improvement in FST, but not in mobility, visual acuity (VA), or central retinal thickness, while a third systematic review that included the same studies found an improvement of VA and FST for up to 2 years after treatment. One RCT (N=31) comparing voretigene neparvovec with a control demonstrated greater improvements on the MLMT, which measures the ability to navigate in dim lighting conditions. Most other measures of visual function were also significantly improved in the voretigene neparvovec group compared with the control group. Adverse events were mostly mild to moderate; however, there is limited follow-up available, and the long-term efficacy and safety are unknown. Based on a small number of patients from both early and phase 3 studies, voretigene neparvovec appears to have durable effects to at least 4 years. Other gene therapies tested in early phase trials have shown improvements in retinal function but variable durability of effect; some patients from 2 cohorts who initially experienced improvements have subsequently experienced declines after 1 to 3 years. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

National Institute for Health and Care Excellence (NICE)

In 2019, NICE published guidance for the use of voretigene neparvovec (Luxturna) in the treatment of inherited retinal dystrophies caused by *RPE65* gene mutations. (57) The treatment is recommended for individuals with vision loss caused by inherited retinal dystrophy from confirmed biallelic *RPE65* mutations who have sufficient viable retinal cells. Despite uncertainty surrounding long-term durability, the committee felt this intervention is likely to provide important clinical benefits for individuals afflicted with inherited retinal dystrophies.

Ongoing and Unpublished Clinical Trials

Interest in gene therapy for inherited retinal dystrophies has grown enormously in recent years; numerous gene therapy treatments (with various targets) are now in different stages of clinical development. Some currently ongoing and unpublished trials that might influence this policy are listed in Table 6.

Table 6. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
NCT04123626[a]	A Prospective First-In-Human Study to Evaluate the Safety and Tolerability of QR-1123 in Subjects With Autosomal Dominant Retinitis Pigmentosa (adRP) Due to the P23H Mutation in the RHO Gene (AURORA)	11	Jun 2022 (ongoing; last updated May 2022)
NCT03913143[a]	Double-masked, Randomized, Controlled, Multiple-dose Study to Evaluate Efficacy, Safety, Tolerability and Syst. Exposure of QR-110 in Leber's Congenital Amaurosis (LCA) Due to c.2991+1655A>G Mutation (p.Cys998X) in the CEP290 Gene (ILLUMINATE)	36	Mar 2023 (ongoing; last updated Mar 2022)
NCT04671433[a]	Phase 3 Randomized, Controlled Study of AAV5-RPGR for the Treatment of X-linked Retinitis Pigmentosa Associated With Variants in the RPGR Gene	97 (actual)	Sep 2024
NCT03597399[a]	A Post-Authorization, Multicenter, Longitudinal, Observational Safety Registry Study for Patients Treated With Voretigene Neparvovec in US	87	Sept 2025
NCT03328130[a]	Safety and Efficacy of a Unilateral Subretinal Administration of HORA-PDE6B in Patients With Retinitis Pigmentosa	23	Dec 2029 (recruiting)

	Harbouring Mutations in the PDE6B Gene Leading to a Defect in PDE6ß Expression		
NCT03316560[a]	An Open-Label Dose Escalation Study to Evaluate the Safety and Efficacy of AGTC-501 (rAAV2tYF-GRK1-RPGR) in Subjects With X-linked Retinitis Pigmentosa Caused by RPGR Mutations	29 (actual)	Mar 2025
NCT00481546	Phase I Trial of Ocular Subretinal Injection of a Recombinant Adeno-Associated Virus (rAAV2-CBSB-hRPE65) Gene Vector to Patients With Retinal Disease Due to RPE65 Mutations (Clinical Trials of Gene Therapy for Leber Congenital Amaurosis) (LCA)	15	Jun 2026 (ongoing)
NCT04794101[a]	Follow-up Phase 3 Randomized, Controlled Study of AAV5-RPGR for the Treatment of X-linked Retinitis Pigmentosa Associated With Variants in the RPGR Gene	97 (actual)	Sep 2029
NCT04517149[a]	An Open-Label, Phase 1/2 Trial of Gene Therapy 4D-125 in Males With X-linked Retinitis Pigmentosa (XLRP) Caused by Mutations in the RPGR Gene	21 (actual)	May 2029 (ongoing)
NCT00999609[a]	A Safety and Efficacy Study in Subjects With Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 to the Retinal Pigment Epithelium (RPE) [AAV2-hRPE65v2-301]	31	Jan 2030 (ongoing)
NCT03602820[a]	A Long-Term Follow-Up Study in Subjects Who Received an Adenovirus-Associated Viral Vector Serotype 2 Containing the Human RPE65 Gene (AAV2-hRPE65v2, Voretigene Neparvovec-rzyl) Administered Via Subretinal Injection	41	Jan 2030 (ongoing)
NCT01208389[a]	A Follow-On Study to Evaluate the Safety of Re-Administration of Adeno-Associated Viral Vector Containing the Gene for Human RPE65 [AAV2-hRPE65v2] to the Contralateral Eye in Subjects With Leber Congenital Amaurosis (LCA) Previously Enrolled in a Phase 1 Study	12	Oct 2027 (ongoing)
NCT02435940	Foundation Fighting Blindness Registry, My Retina Tracker	20,000	Jun 2037 (recruiting)

NCT02946879[a]	Long-term Follow-up Study of Participants Following an Open-Label, Multi-centre, Phase I/II Dose Escalation Trial of an Adeno-associated Virus Vector (AAV2/5-OPTIRPE65) for Gene Therapy of Adults and Children With Retinal Dystrophy Owing to Defects in RPE65 (LCA2)	14	Jun 2023 (completed)

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	67299, 0810T
HCPCS Codes	J3398

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
08/01/2026	Document updated. Coverage unchanged. References 53 and 54 added; others updated.
10/01/2025	Document updated with literature review. The following change was made to Coverage: Medical necessity criteria was modified, with movement of some content to Policy Guidelines section. Added references 21, 32, and 54.
12/15/2024	Reviewed. No changes.
08/01/2023	Document updated with literature review. The following change was made in Coverage: updated term “patient” to “individual” although no change to intent of Coverage. Added references 2, 12, 22, 24, 29, 30. Others updated; some removed.
06/01/2022	Document updated with literature review. Coverage unchanged. Added references 22, 23, 47, 49, 50. Others updated.
08/01/2021	Reviewed. No changes.

07/15/2020	Document updated with literature review. The following change was made to coverage: 1) Added age <65 years added; 2) Expanded genetic testing criteria to include a) Single *RPE65* pathogenic variant or likely pathogenic variant found in the homozygous state (e.g., the presence of the same variant in both copies alleles of the *RPE65* gene), b)Two *RPE65* pathogenic variants or likely pathogenic variants found in the trans configuration (compound heterozygous state) by segregation analysis (e.g., the presence of 2 different *RPE65* variants in separate copies of the *RPE65* gene (trans configuration); 3) Expanded presence of viable retinal cells criteria to also include a) ≥3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole, or b) Remaining VF within 30° of fixation as measured by III4e isopter or equivalent; 4) Added that patient does not have ANY of the following: a) Pregnancy in females, b) Breastfeeding, c) Use of retinoid compounds or precursors that could potentially interact with the biochemical activity of the *RPE65* enzyme; individuals who discontinue use of these compounds for 18 months may become eligible, d) Prior intraocular surgery within 6 months, e) Preexisting eye conditions or complicating systemic diseases that would preclude the planned surgery or interfere with the interpretation of study with examples. All new references. Title changed from "Voretigene Neparvovec (Luxturna)."
06/01/2018	New medical document. Voretigene neparvovec (Luxturna™) may be considered medically necessary for the treatment of inherited retinal dystrophies (IRD) caused by mutations in the retinal pigment epithelium-specific protein 65kDa (RPE65) gene in patients who meet ALL the following criteria: Patient is greater than 12 months of age; Diagnosis of a confirmed biallelic RPE65 mutation-associated retinal dystrophy (e.g. Leber's congenital amaurosis [LCA], retinitis pigmentosa [RP] early onset severe retinal dystrophy [EOSRD], etc.); Genetic testing documenting biallelic mutations of the RPE65 gene; Sufficient viable retinal cells as determined by optical coherence tomography (OCT) confirming an area of retina within the posterior pole of >100 µm thickness; Prescribed and administered by ophthalmologist or retinal surgeon with experience providing sub-retinal injections; Patient has not previously received RPE65 gene therapy in intended eye. Voretigene neparvovec (Luxturna™) is considered experimental, investigational, and/or unproven for all other indications.